The Impact of Cardiovascular Risk Factors on Aortic Stiffness and Wave Reflections Depends on Age: The Anglo-Cardiff Collaborative Trial (ACCT III)

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Hypertension. 2010;56:591-597; originally published online August 9, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.156950
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Abstract—Ageing exerts differential effects on arterial stiffness and wave reflections. However, the impact of cardiovascular risk factors on arterial stiffness and wave reflections and, particularly, how such effects are influenced by ageing has not been assessed within a single large population, covering a sufficiently wide age range. Therefore, we determined the extent to which age alters the impact of traditional cardiovascular risk factors on arterial stiffness and wave reflections. Aortic stiffness and wave reflections were assessed in 4421 individuals (age range 18 to 92 years). When treated as continuous variables, clinic systolic, diastolic, and pulse pressures and glucose levels were independently associated with stiffness, and, with the exception of diastolic pressure, these associations were more marked in older individuals. In contrast, clinic systolic and diastolic pressures and smoking were independently associated with wave reflections, with stronger associations observed in younger individuals. The impact of traditional cardiovascular risk factors on arterial stiffness and wave reflections is strongly dependent on age and is largely driven by blood pressure. Additional studies are required to assess the impact of these arterial measures on cardiovascular outcome within a single population. **(*Hypertension*. 2010;56:591-597.)**

Key Words: aortic stiffness ■ wave reflections ■ cardiovascular risk ■ vascular ageing

Ageing exerts a marked influence on the cardiovascular system. One of the more apparent effects is large artery stiffening or arteriosclerosis,[1] which is now recognized as a key, independent determinant of cardiovascular risk.[2] In addition, increased arterial wave reflections also predict outcome in several patient groups.[2] We recently reported[3] a nonlinear relationship between healthy ageing and 2 commonly used indices of large artery hemodynamics: aortic pulse wave velocity (aPWV), a direct measure of arterial stiffness, and aortic augmentation index (AIx), a composite measure of wave reflections. In particular, the age-related changes in aPWV were significantly greater in individuals ≥50 years of age, whereas the changes in AIx were more marked in younger individuals. This led us to hypothesize that aPWV may provide a more sensitive indication of arterial ageing in older individuals, whereas AIx may be a more sensitive marker in younger individuals, although this hypothesis[3] remains to be tested.

Interestingly, increased arterial stiffness has been reported in individuals with cardiovascular risk factors such as hypertension,[4–6] hypercholesterolemia,[7–9] cigarette smoking,[10–12] and diabetes,[13–15] leading to the popular concept that such individuals may experience premature vascular ageing in relation to healthy individuals. However, these studies have used a wide variety of methodologies to assess arterial stiffness, in relatively small populations of differing ages, leading to inconsistent findings. A recent systematic review suggested that age and blood pressure (BP) explain the majority of the observed variance in arterial stiffness, with other factors having little or no effect.[16] However, as yet, there has been no systematic analysis of the relative impact of cardiovascular risk factors on large artery properties, conducted within a single population, covering a sufficiently wide age range. Moreover, the extent to which ageing alters the effect of cardiovascular risk factors on arterial stiffness and wave reflections has not been well described.

The aim of the present study was to determine the relative impact of cardiovascular risk factors on arterial stiffness and wave reflections in a large cohort of individuals from the Anglo-Cardiff Collaborative Trial (ACCT) and how this is affected by ageing. Specifically, we wished to test the hypothesis that cardiovascular risk factors have a greater

Received May 21, 2010; first decision June 6, 2010; revision accepted July 13, 2010.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.110.156950**

impact on wave reflections in younger individuals but a greater impact on aortic stiffness in older individuals.

Methods

Subjects were drawn from the ACCT study population, which consists of ≈12 000 individuals, selected at random from local general practice lists and open-access cardiovascular risk assessment clinics, across East Anglia and Wales. The overall response rate was 85%. Subjects with secondary forms of hypertension or overt cardiovascular disease were excluded, yielding a total of 4421 individuals for whom hemodynamic and biochemical data were complete at the time of analysis.

Individuals were grouped according to the presence of the following cardiovascular risk factors based on past history or confirmed at the time of screening: hypertension (documented or brachial systolic BP ≥140 mm Hg or brachial diastolic BP ≥90 mm Hg); hypercholesterolemia (documented or fasting total cholesterol >6.2 mmol/L); current smoking (>1 cigarette per day); diabetes mellitus (World Health Organization criteria) but without cardiovascular disease. The presence of the metabolic syndrome was defined following guidelines from the International Diabetes Federation.[17] Approval for all studies was obtained from the local research ethics committees, and written informed consent obtained from each participant.

Hemodynamics

BP was recorded in the dominant arm using a validated oscillometric technique (HEM-705CP; Omron Corporation). Radial artery waveforms were recorded with a high-fidelity micromanometer (SPC-301; Millar Instruments) from the wrist of the dominant arm. Pulse wave analysis (SphygmoCor; AtCor Medical) was then used to generate a corresponding central (ascending aortic) waveform using a generalized transfer function,[18] which has been prospectively validated for the assessment of ascending aortic BP.[19,20] Using the integral software, augmented pressure was calculated as the difference between the second and first systolic peaks, and AIx was calculated as augmented pressure expressed as a percentage of the pulse pressure. Heart rate was determined from the aortic waveform, and mean arterial pressure (MAP) was obtained by integration of the waveform.

The aPWV was measured using the same device by sequentially recording ECG-gated carotid and femoral artery waveforms, as described in detail previously.[21] Path length for the determination of aPWV was measured as the surface distance between the suprasternal notch and femoral site minus the distance between the suprasternal notch and carotid site using a tape measure. 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 aPWV were in agreement with our previously published data.[21]

Protocol

Height and weight were assessed, and a medical history questionnaire including details of medication was completed. After 10 minutes of seated rest, brachial BP (clinic BP) and radial artery waveforms were recorded in all subjects. After an additional 15 minutes of supine rest, brachial BP and radial artery waveforms were remeasured and aPWV determined. Then 10 mL of blood was drawn from the antecubital fossa into plain tubes. The samples were centrifuged at 4°C (4000 rpm for 20 minutes) and the serum separated and stored at −80°C for subsequent analysis. Cholesterol, triglycerides, and glucose were determined using standard methodology in an accredited laboratory.

Data Analysis

Data were analyzed using SPSS software (version 12.0). To explore the associations between traditional cardiovascular risk factors and aPWV and AIx, 2 approaches were used. First, univariable and stepwise multivariable regression models were constructed using the entire study population and treating risk factors as dichotomous (yes/no) variables. Then, using only untreated individuals, additional stepwise multivariable regression models were constructed, treating cardiovascular risk factors as continuous variables. Finally, the influence of age on the relationship between cardiovascular risk factors and arterial hemodynamics was examined by constructing stepwise multivariable models including age×risk factor interaction terms. Unless otherwise stated, aPWV has been adjusted for age, gender, and MAP, and AIx has been adjusted for age, gender, height, and heart rate. Where >1 component of BP was included in a multivariable model, collinearity was assessed by the tolerance statistic provided by SPSS, following Menard.[22] All values represent means±SD unless stated, and a P value <0.05 was considered significant.

Table 1. Characteristics of Subjects Included in the Analyses

Parameter	All n=4421	Untreated n=3613
Age, y	46±23	41±22
Age range, y	18–92	18–92
Gender, male/female	2529/1892	1991/1622
Height, m	1.70±0.09	1.71±0.09
Weight, kg	75±15	73±15
Body mass index, kg/m^2	25.6±4.6	25.0±4.38
Current smoker, %	17	15
Seated (clinic) SBP, mm Hg	131±20	128±19
Seated (clinic) DBP, mm Hg	78±11	78±11
Seated heart rate, bpm	72±12	72±12
Supine MAP, mm Hg	92±14	90±13
Supine heart rate, bpm	67±11	67±11
Supine augmentation index, %	17±18	14±18
Aortic PWV, m/s	7.92±2.99	7.34±2.66
Total cholesterol, mmol/L	4.72±1.15	4.65±1.16
LDL, mmol/L	2.71±0.97	2.67±0.98
HDL, mmol/L	1.42±0.40	1.43±0.40
Triglycerides, mmol/L	1.38±0.94	1.29±0.88
Glucose, mmol/L	5.19±1.56	5.00±1.24
Vasoactive therapy, %	18	…
Statin therapy, %	6	…

Data are means±SD. SBP indicates systolic BP; DBP, diastolic BP.

Results

The demographic and hemodynamic characteristics of the study population are shown in Table 1 for all individuals and for those not receiving medication.

Risk Factors as Dichotomous Variables

Traditional cardiovascular risk factors (hypertension, hypercholesterolemia, smoking, and diabetes) were initially treated as dichotomous (yes/no) variables, and the demographic and hemodynamic characteristics were compared between individuals with and without each factor (Table 2). Because of risk factor clustering, individuals with a designated risk factor (eg, hypertension or smoking) were also more likely to have increased levels of other risk factors (eg, higher total cholesterol or glucose). After adjusting for confounding factors, aPWV was significantly elevated in hypertensives, smokers, and diabetics, whereas AIx was significantly elevated in hypertensives, hypercholesterolemics, and smokers. More-

Table 2. Characteristics of Individuals With and Without Traditional Cardiovascular Risk Factors

	Hypertension		Hypercholesterolemia		Smoking		Diabetes	
Parameter	Yes (n=1827)	No (n=2594)	Yes (n=779)	No (n=3642)	Yes (n=733)	No (n=3688)	Yes (n=206)	No (n=4215)
Age, years	59±19‡	36±21	62±14‡	42±23	53±23‡	44±23	64±16‡	45±23
Gender, % male	67‡	50	49‡	59	72‡	54	66†	57
Current smokers, %	20‡	14	16‡	17	100‡	0	26‡	16
Body mass index, kg/m^2	27.7±4.6‡	24.2±4.1	27.6±4.8	25.2±4.4	26.2±4.23‡	25.5±4.7	29.4±5.5‡	25.5±4.5
Clinic SBP, mm Hg	148±17‡	119±11	140±20‡	129±19	134±19‡	130±20	142±18‡	130±20
Clinic DBP, mm Hg	85±12‡	74±8	82±11‡	77±11	77±11†	78±11	80±11*	78±11
aPWV, m/s§	8.04±3.07‡	7.61±1.94	7.66±2.24	7.80±2.81	8.00±3.34‡	7.74±2.74	8.97±3.67‡	7.87±2.88
AIx, %¶	17.5±14.7‡	14.6±17.7	17.0±13.4†	15.5±17.9	16.9±16.7†	15.5±18.3	17.0±12.4	16.3±18.1
Total cholesterol, mmol/L	5.10±1.12‡	4.46±1.09	5.93±1.28‡	4.44±0.92	4.78±1.11	4.70±1.16	4.70±1.04	4.72±1.15
Glucose, mmol/L	5.62±1.97‡	4.90±1.12	5.49±1.90‡	5.12±1.46	5.64±2.11‡	5.10±1.41	8.75±4.10‡	5.00±1.00

SBP indicates systolic BP; DBP, diastolic BP.
*$P<0.05$, †$P<0.01$, and ‡$P<0.001$ vs individuals without the risk factor.
§Adjusted for age, gender, and MAP; ¶adjusted for age, gender, height, and heart rate.

over, individuals defined as having the metabolic syndrome had a significantly elevated aPWV (8.49±1.31 m/s versus 8.17±2.14 m/s; $P<0.001$) and AIx (19±14% versus 16±13%; $P=0.02$) compared with those without the metabolic syndrome (data not shown).

To compare the relative influence of each risk factor on aPWV and AIx, univariable and multivariable analyses were conducted. After initial adjustment for age and gender, the presence of hypertension, smoking, and diabetes was associated with aPWV (Table 3). In a fully adjusted multivariable model, diabetes, hypertension, and current smoking all remained positively and independently associated with a PWV, together with age, MAP, heart rate, and statin therapy. Gender and hypercholesterolemia were inversely associated with aPWV. Hypertension, hypercholesterolemia, and current smoking were all positively associated with AIx in univariable analyses. All 3 risk factors remained independently associated with AIx in a fully adjusted model, together with age, gender, heart rate mean pressure, and height, although the associations between AIx and heart rate, height, and hypertension were inverse. Tolerance statistics indicated that collinearity between variables fell within acceptable limits (data not shown).

Risk Factors as Continuous Variables

Risk factors were then treated as continuous rather than dichotomous variables. In addition, only untreated individuals were included in additional analyses. This approach allowed us to examine more fully the associations between individual risk factors and arterial hemodynamics while minimizing the potentially confounding influences of risk factor clustering and medication on arterial hemodynamics (Table 4). In fully adjusted models, clinic systolic BP and

Table 3. Univariable and Multivariable Regression Models for PWV and AIx, Considering Risk Factors as Dichotomous Variables

aPWV	Beta	R^2 Change	P	AIx	Beta	R^2 Change	P
Univariable models				Univariable models			
Age, gender	…	…	<0.001	Age, gender, height, HR	…	…	<0.001
Hypertension, yes/no	0.20	…	<0.001	Hypertension (yes/no)	0.08	…	<0.001
Hypercholesterolemia, yes/no	0.01	…	0.3	Hypercholesterolemia (yes/no)	0.04	…	<0.001
Smoking, yes/no	0.04	…	<0.001	Smoking (yes/no)	0.03	…	0.001
Diabetes, yes/no	0.08	…	<0.001	Diabetes (yes/no)	0.01	…	0.3
Multivariable model, adjusted R^2= 0.68				Multivariable model, adjusted R^2= 0.74			
Age	0.61	60.7	<0.001	Age	0.61	61	<0.001
MAP	0.19	4.6	<0.001	Gender	0.17	4.3	<0.001
Heart rate	0.10	0.8	<0.001	Heart rate	−0.24	3.3	<0.001
Gender	−0.08	0.8	<0.001	MAP	0.31	4.7	<0.001
Diabetes, yes/no	0.07	0.6	<0.001	Height	−0.12	0.8	<0.001
Hypertension, yes/no	0.06	0.2	<0.001	Hypertension (yes/no)	−0.06	0.2	<0.001
Smoker, yes/no	0.03	0.1	0.003	Smoker (yes/no)	0.03	0.1	0.002
Statin therapy, yes/no	0.03	<0.1	0.007	Hypercholesterolemia (yes/no)	0.02	0.1	0.004
Hypercholesterolemia, yes/no	−0.02	0.1	0.008				

Variables excluded: vasoactive therapy (aPWV); diabetes, statins, and vasoactive therapy (AIx).

Table 4. Multivariable Regression Models for PWV and AIx in Untreated Individuals, Considering Risk Factors as Continuous Variables

aPWV	Beta	R^2 Change	*P*	AIx	Beta	R^2 Change	*P*
Adjusted R^2=0.71				Adjusted R^2= 0.73			
Age	0.61	63.1	<0.001	Age	0.60	59.9	<0.001
Clinic SBP	0.16	5.4	<0.001	Gender	0.13	4.0	<0.001
Heart rate	0.08	0.9	<0.001	MAP	0.38	3.0	<0.001
MAP	0.22	0.5	<0.001	Heart rate	−0.22	4.1	<0.001
Clinic DBP	−0.12	0.8	<0.001	Clinic systolic BP	−0.20	1.4	<0.001
Glucose	0.06	0.4	<0.001	Height	−0.12	0.7	<0.001
Gender	−0.06	0.3	<0.001	Clinic diastolic BP	0.06	0.1	<0.001
				Smoking	0.03	0.1	0.001
Age×risk factor interactions*				Age×risk factor interactions*			
Age×clinic SBP	1.18	69.9	<0.001	Age×clinic SBP	−0.47	1.6	<0.001
Age×clinic DBP	−0.21	63.7	0.01	Age×clinic DBP	−0.35	0.2	<0.001
Age×clinic PP	0.72	67.1	<0.001	Age×smoking	−0.06	<0.1	0.03
Age×glucose	0.34	1.2	<0.001	Age×total cholesterol	0.01	…	0.8
Age×smoking	0.01	…	0.2	Age×glucose	−0.04	…	0.6
Age×total cholesterol	0.01	…	0.9				

SBP indicates systolic BP; DBP, diastolic BP; PP, pulse pressure.
Variables excluded: Height, weight, smoking, and total cholesterol (aPWV) and weight, total cholesterol, and glucose (AIx).
*Age×risk factor interactions are summarized here. Full risk factor interaction models appear in a supplemental table (http://hyper.ahajournals.org).

glucose levels were positively and independently associated with aPWV, along with age, heart rate, and MAP. Clinic diastolic BP was inversely associated with aPWV together with gender. In contrast, clinic diastolic pressure and smoking were positively and independently associated with AIx, together with age, gender, and MAP, whereas clinic systolic pressure was inversely associated with AIx, together with heart rate and height. Again, the extent of collinearity between variables fell within acceptable limits (data not shown).

Influence of Age on the Relationship Between Risk Factors and aPWV and AIx

Using the same subset of untreated individuals, the influence of age on the relationship between risk factors and aPWV and AIx was then explored in a series of multivariable regression models that included age×risk factor interaction terms (online supplement, available at http://hyper.ahajournals.org). As summarized in Table 4, there were significant interactions between age and clinic systolic pressure, diastolic pressure, pulse pressure, and glucose levels for aPWV. For AIx, there were significant interactions between age and clinic systolic pressure, diastolic pressure, and smoking. These interactions are represented graphically in Figures 1 (aPWV) and 2 (AIx). As illustrated in Figure 1, clinic systolic BP, pulse pressure, and glucose were more strongly associated with aPWV in older individuals, whereas the association with diastolic BP was stronger in younger subjects. Figure 2 shows that the associations between AIx and clinic systolic and diastolic BP and smoking were more marked in younger individuals.

Discussion

We demonstrated in a single large population covering a wide age range that BP exerts the most powerful influence on arterial stiffness and wave reflections, but that traditional cardiovascular risk factors have a much more modest effect that is substantially influenced by age. Whereas BP and glucose levels had a greater effect on arterial stiffness in older individuals, BP and smoking had a greater effect on wave reflections in younger individuals. These findings confirm and extend our previous observations that arterial stiffness and wave reflections are differentially affected by ageing.

The relationship between traditional cardiovascular risk factors and large artery hemodynamics has been studied widely in the past. Valuable cross-sectional data has been provided by studies in hypertensives,[6,23–32] chronic cigarette smokers,[11,12,33,34] asymptomatic individuals with hypercholesterolemia[9] and type I and type II diabetics,[13–15,35–37] and in relation to cholesterol[38–42] and blood glucose levels.[43] However, the findings from these studies have been inconsistent as a result of small sample sizes, differing ages, variation in the methodologies used to assess large artery properties, and the lack of appropriate controls for confounding factors. Moreover, none of these studies considered whether ageing alters the relationship between cardiovascular risk factors and various arterial properties. Mitchell et al[44] previously examined the prevalence and correlates of "abnormal" arterial stiffness in pooled samples from the Framingham Heart Study using an age-specific threshold criteria (>90th percentile for stiffness measures) derived from a reference sample of healthy individuals. The authors observed that aPWV was increased in 21% of men and 23% of women, and that the major correlates of arterial stiffness were increased MAP, abnormal glucose metabolism, lipid abnormalities, and obesity. However, the average age of the pooled sample was ≈63 years, and no age-specific information concerning the prevalence of abnormal stiffness in individuals <50 years of age was provided. Moreover, the impact of cardiovascular risk factors on wave reflections was not studied.

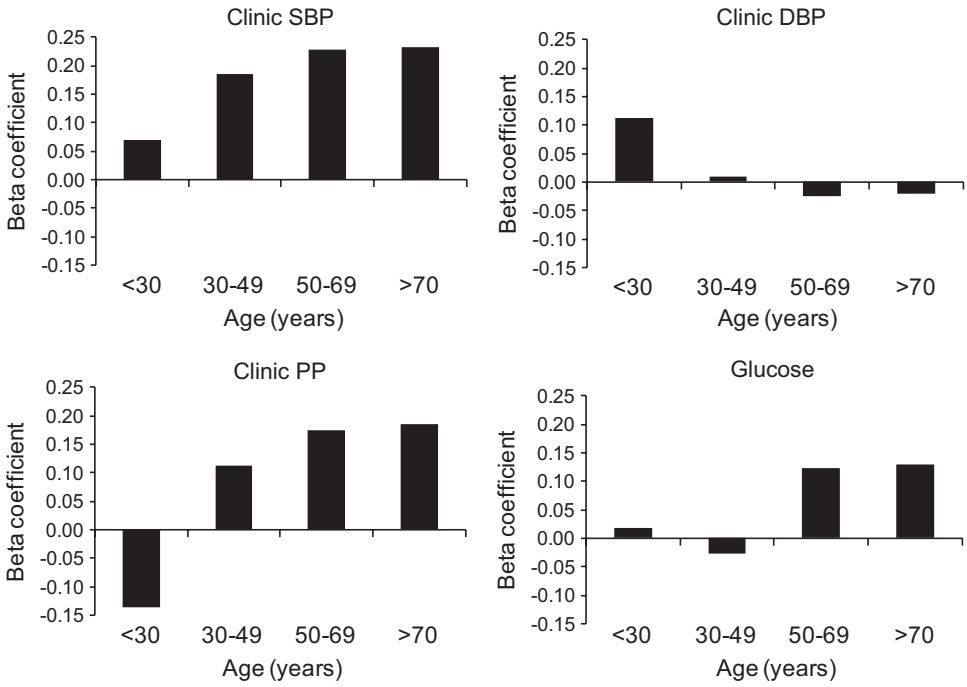

Figure 1. Bar graphs representing the influence of age on the relationship between risk factors and aPWV. The bars represent standardized beta coefficients for the relationship between each risk factor and aPWV after adjustment for age, gender, and MAP. SBP indicates systolic BP; DBP, diastolic BP; PP, pulse pressure.

In the current study, when risk factors were considered dichotomous variables, aPWV was elevated in hypertensives, smokers, and diabetics, and the presence of these risk factors remained positively and independently associated with aPWV in multivariable analyses. In contrast, AIx was elevated in hypertensives, hypercholesterolemics, and smokers, and again, these factors all remained independently associated with AIx in multivariable analyses, although the residual association with hypertension was inverse. This may reflect a predominant influence of isolated systolic hypertension, which is the most common form of hypertension in young adults and also those >60 years of age. Lower values of AIx have been reported previously in young individuals with isolated systolic hypertension, [45] and in older individuals, AIx

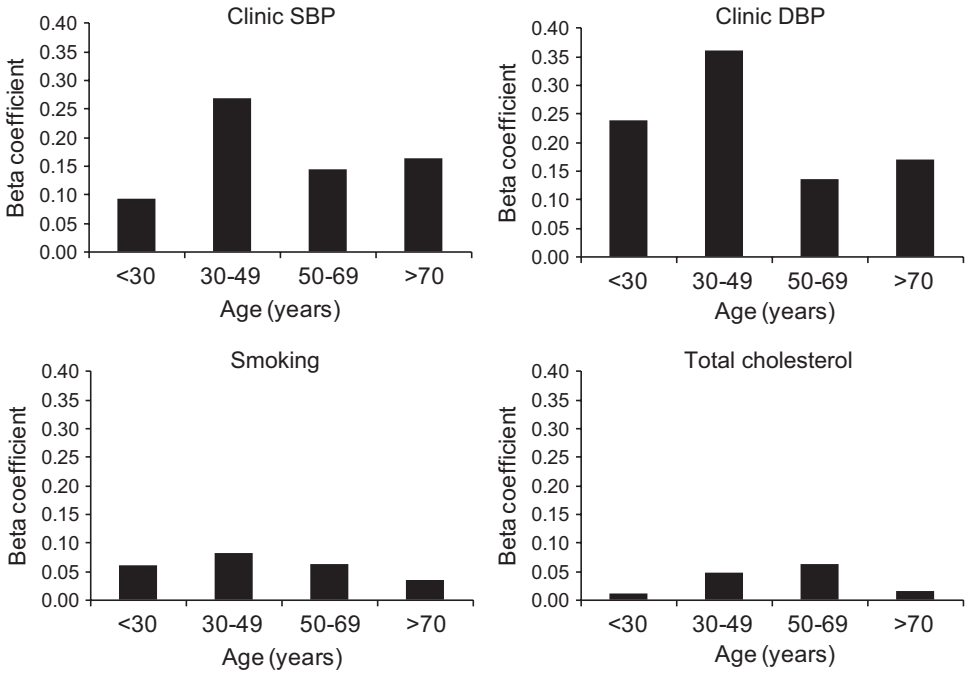

Figure 2. Bar graphs representing the influence of age on the relationship between risk factors and AIx. The bars represent standardized beta coefficients for the relationship between each risk factor and AIx after adjustment for age, gender, height, and heart rate. SBP indicates systolic BP; DBP, diastolic BP.

is similar between patients with isolated systolic hypertension and healthy controls.[6] Nevertheless, our data are in agreement with a wealth of previous studies in which risk factors have been treated as dichotomous variables. However, as noted many times previously, risk factors tend to cluster, even in low-risk individuals.[46] Indeed, in the current study, >20% of individuals had ≥2 cardiovascular risk factors. This is important because defining the presence or absence of risk factors by applying arbitrary criteria makes it very difficult to determine the true nature of the associations between individual risk factors and arterial properties.

To minimize the possible effects of risk factor clustering and investigate more fully the influence of risk factors on arterial properties, individual risk factors were then treated as continuous rather than discrete variables. In addition, limiting the analyses to those individuals not on drug therapy excluded the potentially confounding influence of drugs on arterial properties. After adjusting for confounding factors, clinic systolic and diastolic pressures and glucose levels were independently associated with aPWV, whereas clinic systolic and diastolic pressures and smoking were independently associated with AIx. However, age and BP were most strongly associated, accounting for ≈70% and 65% of the explained variance in aPWV and AIx, respectively, with the other cardiovascular risk factors having relatively little influence in either model. Overall, these observations underline the dominant influence of age and BP in defining arterial properties. Moreover, they provide direct empirical support for the findings of a recent systematic review[16] that suggested that other than BP, the impact of traditional cardiovascular risk factors on arterial stiffness was relatively modest.

Ageing exerts one of the most powerful influences on arterial properties. However, our previous findings suggest that there is a differential effect of age on arterial stiffness and wave reflections, with a steeper age-related rise in aPWV in older individuals and a steeper age-related rise in AIx in younger individuals.[3] In the current study, we extended these findings by demonstrating a significant influence of age on the relationship between risk factors and arterial stiffness and wave reflections. The independent associations between aPWV and clinic systolic BP, pulse pressure, and glucose were all more marked in older individuals, although diastolic BP was more strongly related to aPWV in younger subjects. One potential explanation for these findings is that over time, progressive aortic stiffening drives a decrease in diastolic pressure and an increase in systolic and pulse pressure. Indeed, as stated previously, isolated systolic hypertension is a common condition in older individuals and one that is characterized by increased aortic stiffening.[6] In contrast to the findings with aPWV, the associations between AIx and clinic systolic and diastolic BP and smoking were all more marked in younger individuals. Interestingly, outcome data from the Framingham Heart Study[47] support the view that aPWV is a potent driver of cardiovascular risk in middle-aged and older individuals, whereas AIx does not appear to be as strongly related in this age group. Together, these findings suggest that age exerts a differential effect on arterial hemodynamics. In keeping with this observation, BP and other traditional cardiovascular risk factors have a greater impact on wave reflections in younger individuals but a greater impact on aPWV in older individuals.

The present study has several limitations. First, the findings are based on cross-sectional analyses, and longitudinal data are clearly required to confirm the extent to which ageing influences the impact of cardiovascular risk factors on arterial hemodynamics. In addition, we cannot exclude the possibility that increased arterial stiffness or wave reflections predisposes certain individuals to the development of cardiovascular risk factors or that risk factors and arterial measures are both surrogate markers of underlying causal mechanisms.

Perspectives

Arterial stiffness and wave reflections and their relationship with cardiovascular risk have been the focus of much recent research. Arterial measures such as aPWV and AIx, which are widely used to quantify aortic stiffness and wave reflections, are noninvasive, easy to use, and do not require calibration, making them ideal for routine clinical use. Many previous studies explored the links between arterial properties and traditional cardiovascular risk factors using defined groups of patients such as hypertensives or hypercholesterolemics. However, the findings of these studies are difficult to interpret because of the inherent confounding effects of risk factor clustering. We explored the continuous relationship between risk factors and arterial properties in a large cohort of individuals across a wide spectrum of age and have demonstrated that the impact of traditional cardiovascular risk factors on arterial stiffness and wave reflections is strongly dependent on age and is driven predominantly by BP. Additional outcome studies are required to confirm the differential impact of these arterial measures on cardiovascular risk within a single population.

Acknowledgments

The ACCT Study Investigators: Samantha Benedict, John Cockcroft, Zahid Dhakam, Stacey Hickson, Julia Howard, Kaisa Maki-Petaja, Barry McDonnell, Carmel McEniery, Karen Miles, Maggie Munnery, Pawan Pusalkar, Christopher Retallick, Chloe Rowe, Ramsey Sabit, James Sharman, Rachel Stainsby, Edna Thomas, Sharon Wallace, Ian Wilkinson, Susannah Williams, Jean Woodcock-Smith, Yasmin.

Sources of Funding

This work was funded in part through the National Institute for Health Research: Cambridge Biomedical Research Centre and the Comprehensive Local Research Network. C.M.M. is supported by a British Heart Foundation Intermediate Research Fellowship. S.S.H. is supported by the Commonwealth Trust. I.B.W. is supported by a British Heart Foundation Senior Clinical Fellowship.

Disclosures

None.

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;107:139–146.
2. Laurent S, Cockcroft JR, van Bortel LM, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson IB, Struijker Boudier HA. Abridged version of the expert consensus document. *Artery Research*. 2007;1:2–12.
3. 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.
4. McVeigh GE, Brennan G, Cohn JN, Finkelstein S, Hayes R, Johnston D. Reduced vascular compliance as a marker for essential hypertension. *Am J Hypertens*. 1991;4:245–251.
5. Armentano R, Simon A, Levenson J, Nguyen PC, Megnien JL, Pichel R. Mechanical pressure versus intrinsic effects of hypertension on large arteries in humans. *Hypertension*. 1991;18:657–664.
6. Yasmin, Wallace S, McEniery CM, Dakham Z, Pusalkar P, Maki-Petaja K, Ashby MJ, Cockcroft JR, Wilkinson IB. Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25:372.
7. Dart AM, Lancombe F, Yeoh JK, Cameron JD, Jennings GL, Laufer E, Esmore DS. Aortic distensibility in patients with isolated hypercholesterolaemia, coronary artery disease, or cardiac transplantation. *Lancet*. 1991; 338:270–273.
8. Giannattasio C, Mangoni AA, Failla M, Carugo S, Stella ML, Stefanoni P, Grassi G, Vergani C, Mancia G. Impaired radial artery compliance in normotensive subjects with familial hypercholesterolemia. *Atherosclerosis*. 1996;124:249–260.
9. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, Frenneaux MP, Cockcroft JR. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol*. 2002;39:1005–1011.
10. Levenson J, Simon AC, Cambien FA, Beretti C. Cigarette smoking and hypertension. Factors independently associated with blood hyperviscosity and arterial rigidity. *Arteriosclerosis*. 1987;7:572–577.
11. Li H, Srinivasan SR, Berenson GS. Comparison of the measures of pulsatile arterial function between asymptomatic younger adult smokers and former smokers: the Bogalusa Heart Study. *Am J Hypertens*. 2006; 19:897–901.
12. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*. 2003;41:183–187.
13. Wilkinson IB, MacCallum H, Rooijmans DF, Murray GD, Cockcroft JR, McKnight JA, Webb DJ. Increased augmentation index and systolic stress in type 1 diabetes mellitus. *QJM*. 2000;93:441–448.
14. Brooks B, Molyneaux L, Yue DK. Augmentation of central arterial pressure in type 1 diabetes. *Diabetes Care*. 1999;22:1722–1727.
15. Brooks BA, Molyneaux LM, Yue DK. Augmentation of central arterial pressure in type 2 diabetes. *Diabet Med*. 2001;18:374–380.
16. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension*. 2009;54:1328–1336.
17. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469–480.
18. 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;14:160–167.
19. 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;38:932–937.
20. Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J, Garrahy P, Wilkinson IB, Marwick TH. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. *Hypertension*. 2006;47:1203–1208.
21. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens*. 1998;16:2079–2084.
22. Menard S. *Applied Logistic Regression Analysis.* Thousand Oaks, Calif: Sage; 1995.
23. Merillon JP, Fontenier GJ, Lerallut JF. Aortic input impedance in normal man and arterial hypertension: its modification during changes in aortic pressure. *Cardiovasc Res*. 1982;16:646–656.
24. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretic, Experimental and Clinical Principles*. V ed. London: Edward Arnold; 2005.
25. Nichols WW, Nicolini FA, Pepine CJ. Determinants of isolated systolic hypertension in the elderly. *J Hypertens Suppl*. 1992;10:S73–S77.
26. Haynes FW, Ellis LB, Weiss S. Pulse wave velocity and arterial elasticity in arterial hypertension, arteriosclerosis, and related conditions. *Am Heart J*. 1936;4:385–401.
27. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac A-M, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. *Hypertension*. 1995;26:485–490.
28. Ting CT, Chang MS, Wang SP, Chiang BN, Yin FC. Regional pulse wave velocities in hypertensive and normotensive humans. *Cardiovasc Res*. 1990;24:865–872.
29. Hasegawa M, Nagao K, Kinoshita Y, Rodbard D, Asahina A. Increased pulse wave velocity and shortened pulse wave transmission time in hypertension and ageing. *Cardiology*. 1997;88:147–151.
30. Safar ME, Laurent S. Behavior of conduit arteries in hypertension. *Clinical Exp Hypertens*. 1993;15:1033–1045.
31. Dart A, Silagy C, Dewar E, Jennings G, McNeil J. Aortic distensibility and left ventricular structure and function in isolated systolic hypertension. *Eur Heart J*. 1993;14:1465–1470.
32. Mitchell GF, Lacourciere Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, Block AJ, Pfeffer MA. 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;108:1592–1598.
33. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension*. 2007;49:981–985.
34. Yufu K, Takahashi N, Hara M, Saikawa T, Yoshimatsu H. Measurement of the brachial-ankle pulse wave velocity and flow-mediated dilatation in young, healthy smokers. *Hypertens Res*. 2007;30:607–612.
35. Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westerhof N, Stehouwer CD. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. *Hypertension*. 2004;43:176–181.
36. Lacy PS, O'Brien DG, Stanley AG, Dewar MM, Swales PP, Williams B. Increased pulse wave velocity is not associated with elevated augmentation index in patients with diabetes. *J Hypertens*. 2004;22:1937–1944.
37. Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, Kamp O, Westerhof N, Bouter LM, Stehouwer CD. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. *Circulation*. 2003;107:2089–2095.
38. Lebrun CE, van der Schouw YT, Bak AA, de Jong FH, Pols HA, Grobbee DE, Lamberts SW, Bots ML. Arterial stiffness in postmenopausal women: determinants of pulse wave velocity. *J Hypertens*. 2002;20:2165–2172.
39. Czernichow S, Bertrais S, Blacher J, Oppert JM, Galan P, Ducimetiere P, Hercberg S, Safar M, Zureik M. Metabolic syndrome in relation to structure and function of large arteries: a predominant effect of blood pressure. A report from the SU.VI.MAX. Vascular Study. *Am J Hypertens*. 2005;18:1154–1160.
40. Taquet A, Bonithon-Kopp C, Simon A, Levenson J, Scarabin Y, Malmejac A, Ducimetiere P, Guize L. Relations of cardiovascular risk factors to aortic pulse wave velocity in asymptomatic middle-aged women. *Eur J Epidemiol*. 1993;9:298–306.
41. Alagona C, Soro A, Westerbacka J, Ylitalo K, Salonen JT, Salonen R, Yki-Jarvinen H, Taskinen MR. Low HDL cholesterol concentration is associated with increased intima-media thickness independent of arterial stiffness in healthy subjects from families with low HDL cholesterol. *Eur J Clin Invest*. 2003;33:457–463.
42. Dart AM, Gatzka CD, Cameron JD, Kingwell BA, Liang YL, Berry KL, Reid CM, Jennings GL. Large artery stiffness is not related to plasma cholesterol in older subjects with hypertension. *Arterioscler Thromb Vasc Biol*. 2004;24:962–968.
43. Salomaa V, Riley W, Kark J, Nardo C, Folsom A. Non-insulin dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. *Circulation*. 1995; 91:1432–1443.
44. Mitchell GF, Guo CY, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. *Circulation*. 2007;115: 2628–2636.
45. McEniery CM, Yasmin, Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, Retallick C, Franklin SS, Brown MJ, Lloyd RC, Cockcroft JR, Wilkinson IB. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension*. 2005;46:221–226.
46. Haffner SM, Ferrannini E, Hazuda HP, Stern MP. Clustering of cardiovascular risk factors in confirmed prehypertensive individuals. *Hypertension*. 1992;20:38–45.
47. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511.

On-Line Supplement

The Impact of Cardiovascular Risk Factors on Aortic Stiffness and Wave Reflections Depends on Age: The Anglo-Cardiff Collaborative Trial (ACCT III)

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S1: Multivariable regression models investigating the influence of age on the relationship between risk factors and aPWV and AIx.

aPWV	Beta	R^2 Change	P	AIx	Beta	R^2 Change	P
Clinic SBP				**Clinic SBP**			
Age x clinic SBP	**1.18**	**69.9**	**<0.001**	Age	0.99	59.9	<0.001
Heart rate	0.08	1.1	<0.001	Gender	0.14	4.0	<0.001
Gender	-0.10	0.9	<0.001	MAP	0.40	3.0	<0.001
MAP	0.18	0.4	<0.001	Heart rate	-0.22	4.1	<0.001
Clinic DBP	-0.06	0.4	<0.001	**Age x clinic SBP**	**-0.47**	**1.6**	**<0.001**
Glucose	0.06	0.3	<0.001	Height	-0.12	0.8	<0.001
Clinic SBP	-0.15	<0.1	<0.001	Smoker	0.03	0.1	0.001
Age	-0.39	0.3	<0.001	Clinic SBP	-0.01	<0.1	0.008
				Clinic DBP	0.03	<0.1	0.029
Clinic DBP				**Clinic DBP**			
Age x clinic DBP	**-0.209**	**63.7**	**0.011**	Age	0.92	59.9	<0.001
Clinic SBP	0.16	2.0	<0.001	Gender	0.14	4.0	<0.001
Age	0.41	2.8	<0.001	MAP	0.38	3.0	<0.001
Heart rate	0.08	0.9	<0.001	Heart rate	-0.22	4.1	<0.001
MAP	0.22	0.5	<0.001	Clinic SBP	-0.19	1.4	<0.001
Clinic DBP	-0.16	0.5	<0.001	Height	-0.12	0.7	<0.001
Glucose	0.06	0.4	<0.001	Clinic DBP	0.13	0.1	<0.001
Gender	-0.06	0.3	<0.001	**Age x DBP**	**-0.35**	**0.2**	**<0.001**
				Smoker	0.03	0.1	0.001
Glucose				**Glucose**			
Age	0.35	63.1	<0.001	Age	0.60	59.9	<0.001
Clinic SBP	0.16	5.4	<0.001	Gender	0.13	4.0	<0.001
Age x Glucose	**0.34**	**1.2**	**<0.001**	MAP	0.38	3.0	<0.001
MAP	0.22	0.8	<0.001	Heart rate	-0.22	4.1	<0.001
Clinic DBP	-0.11	0.5	<0.001	Clinic SBP	-0.20	1.4	<0.001
Heart rate	0.08	0.5	<0.001	Height	-0.12	0.7	<0.001
Gender	-0.06	0.3	<0.001	Clinic DBP	0.06	0.1	<0.001
Glucose	-0.10	0.2	<0.001	Smoking	0.03	0.1	0.001
				Glucose	-0.01	-	0.5
				Age x Glucose	**-0.04**	**-**	**0.6**
Total Cholesterol				**Total Cholesterol**			
Age	0.60	63.1	<0.001	Age	0.60	59.9	<0.001
Clinic SBP	0.16	5.4	<0.001	Gender	0.13	4.0	<0.001
Heart rate	0.08	0.9	<0.001	MAP	0.38	3.0	<0.001
MAP	0.22	0.5	<0.001	Heart rate	-0.22	4.1	<0.001
Clinic DBP	-0.12	0.8	<0.001	Clinic SBP	-0.20	1.4	<0.001
Glucose	0.06	0.4	<0.001	Height	-0.12	0.7	<0.001
Gender	-0.06	0.3	<0.001	Clinic DBP	0.06	0.1	<0.001
Cholesterol	-0.007	-	0.6	Smoking	0.03	0.1	0.001
Age x Cholesterol	**0.006**	**-**	**0.9**	Cholesterol	0.01	-	0.6
				Age x Cholesterol	**0.01**	**-**	**0.8**

aPWV	Beta	R^2 Change	P	AIx	Beta	R^2 Change	P
Smoking				**Smoking**			
Age	0.60	63.1	<0.001	Age	0.61	59.9	<0.001
Clinic SBP	0.16	5.4	<0.001	Gender	0.13	4.0	<0.001
Heart rate	0.08	0.9	<0.001	MAP	0.38	3.0	<0.001
MAP	0.22	0.5	<0.001	Heart rate	-0.22	4.1	<0.001
Clinic DBP	-0.12	0.8	<0.001	Clinic SBP	-0.20	1.4	<0.001
Glucose	0.06	0.4	<0.001	Height	-0.12	0.7	<0.001
Gender	-0.06	0.3	<0.001	Clinic DBP	0.05	0.1	<0.001
Smoking	0.003	-	0.9	Smoking	0.08	0.1	0.001
Age x smoking	**0.013**	**-**	**0.2**	**Age x smoking**	**-0.06**	**<0.1**	**0.03**