The Aging of Elastic and Muscular Arteries

A comparison of diabetic and nondiabetic subjects

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OBJECTIVE — To compare age-related changes in the mechanical properties of different arterial segments in normal volunteers and subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In 169 subjects (diabetic $n = 57$ and nondiabetic $n = 112$), we assessed the mechanical properties of three arterial segments of differing wall composition. Pulse wave velocity (PWV) was measured noninvasively in a thoracoabdominal segment (carotid femoral PWV [PWV_{cf}]), in an upper limb muscular artery (carotid radial PWV [PWV_{cr}]), and from the aorta to the finger (PWV from the aorta to the finger [PWV_{fin}]). Central aortic compliance (CAC) was also measured.

RESULTS — Average CAC was lower (0.662 vs. 0.850, $P < 0.05$) and all measures of PWV tended to be faster in diabetic subjects despite the fact that they were, on average, 10 years younger. However, these measures were not related to age in diabetic subjects. After correcting for blood pressure, only PWV_{cf} was associated with age in nondiabetic subjects ($P < 0.001$). Expressing results as ratios of nonelastic to elastic arterial segments (i.e., PWV_{cr}-to-PWV_{cf} and PWV_{fin}-to-PWV_{cf}) improved the relationship with age. Both PWV_{cr}-to-PWV_{cf} and PWV_{fin}-to-PWV_{cf} were significantly associated with age in nondiabetic subjects ($r = -0.59$, $P < 0.001$; $r = -0.57$, $P < 0.001$) but not in diabetic subjects ($r = -0.15$, $P = 0.302$; $r = -0.24$, $P = 0.129$). Multivariate analysis showed that the ratios were not associated with systolic blood pressure.

CONCLUSIONS — There are significant differences in the rate of age-related decline in vascular stiffness in elastic arteries of nondiabetic compared with diabetic arteries. Diabetic arteries appear to age at an accelerated rate at an earlier age and then reach a functional plateau.

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The mechanical properties of the large conduit arteries are now recognized as an important component of cardiovascular pathophysiology. Less compliant arteries are associated with suboptimal cardiac energy supply-demand balance with reduced subendocardial blood flow and increased left ventricular afterload (1). There are also adverse effects of poor compliance on wave reflection and systolic blood pressure (SBP) (2). It is usually accepted that the age-related increase in SBP and decrease in diastolic blood pressure (DBP) are largely due to decreased proximal aortic compliance, causing more rapid diastolic run-off of a lower-contained volume (hence decreasing DBP) along with an early return of the reflected pressure wave in systole, causing increased pressure augmentation (increased SBP). Thus, increased aortic stiffness is the predominant cause of increased pulse pressure (3).

Pulse pressure is a marker of cardiovascular risk in a general population (4) and, independent of SBP and DBP, has been shown to be a predictor of cardiovascular events (5), particularly in older individuals (6). It has also been shown that aortic stiffness (measured as pulse wave velocity [PWV]) is an independent predictor of cardiovascular risk (7) and all-cause mortality (8) in hypertensive patients. It is therefore probable that increased aortic stiffness is a major factor deleteriously affecting cardiovascular health across all population groups.

It is known that large conduit arteries lose their compliance with advancing age even in the absence of concurrent overt cardiovascular disease. Indeed, in most studies age has been shown to have a predominant effect on indices of arterial mechanical behavior (9). It is also apparent that different arterial segments respond differently to aging, probably related to differences in elastin-collagen smooth-muscle proportions, with most studies showing a much more pronounced relationship of stiffness to age in the more proximal, more elastic, and less muscular arteries (10). In view of this consistent observation, we hypothesized that additional information regarding arterial pathophysiology may be obtained by comparing age-related changes in the mechanical properties of different arterial segments in normal and in diabetic subjects recognized as at increased risk of arterial pathology.

RESEARCH DESIGN AND METHODS

— The study was approved by the institutional ethics committee and performed in accordance with the Declaration of Helsinki. All subjects gave written informed consent.

In 169 subjects (100 men [39 type 2

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Abbreviations: CAC, central aortic compliance; DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure; PWV, pulse wave velocity; PWV_{cf}, carotid femoral PWV; PWV_{cr}, carotid radial PWV; PWV_{fin}, PWV from the aorta to the finger.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Subject demographics and mean results*

	Diabetic subjects	Nondiabetic subjects
Age (years)	61.47 ± 7.37 (44–80)	71.23 ± 11.18* (34–90)
Weight (kg)	79.68 ± 1.81	72.49 ± 1.25*
Height (cm)	168.10 ± 1.13	165.81 ± 0.85
SBP (mmHg)	144.63 ± 2.61	137.36 ± 2.06*
MBP (mmHg)	104.22 ± 1.52	98.45 ± 1.24*
DBP (mmHg)	84.02 ± 1.28	79.00 ± 0.98*
CAC (ACU)	0.662 ± 0.043	0.850 ± 0.056*
PWV_{cf} (ms^{-1})	13.60 ± 0.31	12.77 ± 0.27†
PWV_{cr} (ms^{-1})	11.41 ± 0.19	11.07 ± 0.19
PWV_{fin} (ms^{-1})	5.13 ± 0.073	4.79 ± 0.066*

Data are means ± SE except for age in means ± SD (range). ACU, arbitrary compliance units. †Significantly related to age, $P < 0.05$. *Significant difference between the diabetic and nondiabetic groups, $P < 0.05$.

diabetic] and 69 women [18 type 2 diabetic]), age range 34–90 years, we assessed the mechanical properties of three arterial segments of differing wall composition. PWV was measured using noninvasively accessible superficial pulses and the Complior device (Artech Medicine, Pantin, France) in the predominantly elastic thoraco-abdominal aorta (carotid femoral PWF [PWV_{cf}]) and in an upper-limb muscular artery, over the carotid radial segment (carotid radial PWV [PWV_{cr}]). A different method was used to determine the PWV from the aorta to the finger (PWV_{fin}) by the timing between the R-wave of the electrocardiogram and arrival of the pressure pulse in the index finger (Finapress; Ohmeda) using a purpose-devised software. In addition, as an indicator of left-ventricular load and total systemic arterial compliance, central arterial compliance (CAC) was also assessed.

All methods have been described previously. Briefly, central PWV is determined from the time interval between the identified foot of the carotid and femoral arterial pulse waves and peripheral PWV from the carotid to radial arterial pulse interval (11). Distance was measured using a tape measure between transducer points, as specified by the manufacturer, and the PWV was automatically calculated by the Complior unit. In the case of PWF from the aorta to the finger (PWV_{fin}), distance was taken as that between the suprasternal notch and the tip of the index finger. CAC was assessed from simultaneous measurements of ascending aortic blood velocity using Doppler velocimetry and surrogate estimates of aortic root pressure obtained by applanation tonometry transducer (Millar Instruments, TX) of the proximal right carotid artery. CAC was then derived from the area method described by Liu et al. (12) and previously reported from our laboratory (13).

Statistics

Analysis was performed using SPSS for Windows (release 10.0.5; SPSS, Chicago, IL) with significance taken as $P < 0.05$. The association of parameters with age was investigated by correlation using Pearson's correlation coefficient and univariate linear regression. Differences in association of vascular parameters with age were investigated by comparison of the slope (β) of the appropriate regression lines ($y = \alpha + \beta \times$ age).

RESULTS — Subject demographics and mean results are shown in Table 1. Compared with the nondiabetic subjects, the diabetic group was younger and heavier with increased SBP and DBP. Mean CAC was significantly higher in the nondiabetic group, and PWV_{fin} was significantly lower. Mean PWV_{cf} and PWV_{cr} were not significantly higher in the diabetic group ($P = 0.580$ and $P = 0.233$,

Table 2—*Relationship between measures of arterial compliance and age*

	Nondiabetic subjects	Diabetic subjects
PWV_{fin}		
Correlation	0.053	0.083
Significance (two-tailed)	0.668	0.584
Slope	0.003	−0.006
n	67	46
PWV_{cr}		
Correlation	−0.147	−0.040
Significance (two-tailed)	0.135	0.776
Slope	−0.024	−0.008
n	105	53
PWV_{cf}		
Correlation	0.483	0.116
Significance (two-tailed)	<0.001	0.408
Slope	0.119	0.037
n	106	53
CAC		
Correlation	0.077	−0.064
Significance (two-tailed)	0.440	0.648
Slope	0.004	−0.008
n	103	54
PWV_{fin}-to-PWV_{cf}		
Correlation	−0.571	−0.235
Significance (two-tailed)	<0.001	0.129
Slope	−0.005	−0.002
n	65	43
PWV_{cr}-to-PWV_{cf}		
Correlation	−0.594	−0.149
Significance (two-tailed)	<0.001	0.302
Slope	−0.011	−0.003
n	104	50

Univariate association of PWV, central arterial compliance, and elastic-to-muscular ratios with age for diabetic and nondiabetic subjects.

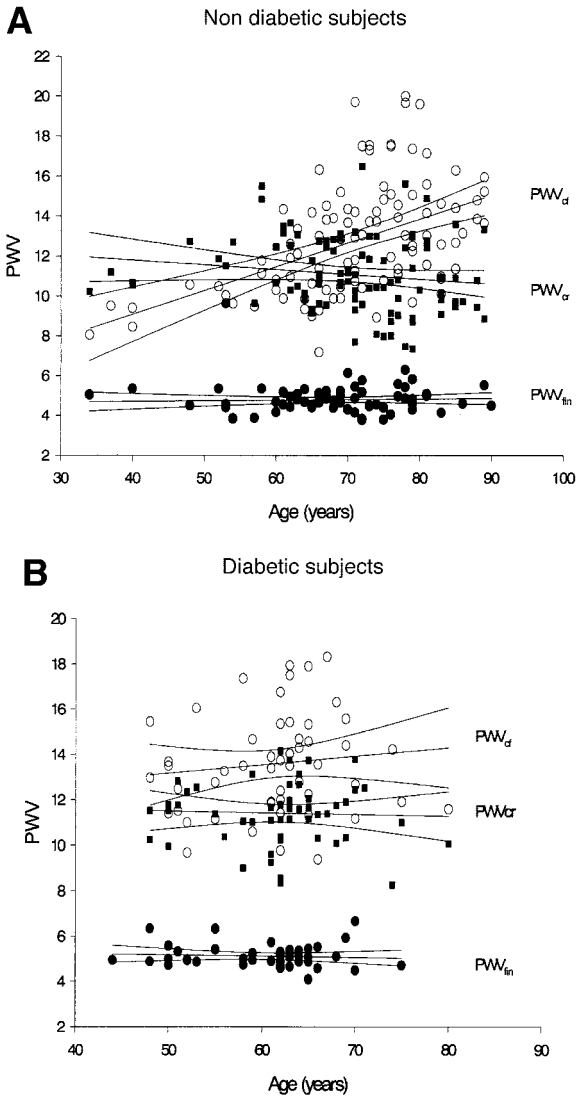

Figure 1—*Association of age and PWV in the elastic carotid femoral segment, the muscular carotid radial segment, and the muscular carotid-finger segment in nondiabetic* (A) *and diabetic* (B) *subjects.* ○, *PWV_{cf}*; ■, *PWV_{cr}*; ●, *PWV_{fin}*.

respectively). Correlations of the measured parameters with age are shown in Table 2, with univariate associations illustrated graphically in Fig. 1. Of note is the disparity of findings between the nondiabetic and diabetic groups. None of the unadjusted measures of arterial stiffness in any segment was associated with age in the diabetic group (β did not differ significantly from zero), whereas PWV_{cf} (β = 0.12 ms^{-1}/year ± 0.021, $P < 0.001$) varied significantly with age in the nondiabetic subjects. Association of specific parameters with blood pressure (DBP, mean blood pressure [MBP], and SBP) varied between groups, but PWV_{cf} and PWV_{fin} were both positively associated with SBP in diabetic and nondiabetic subjects (Table 3). After adjusting for SBP, PWV_{cf} remained significantly correlated with age in the nondiabetic subjects [PWV_{cf} = 0.186 + 0.109 (age) + 0.035 (SBP), r^2 = 0.31, coefficient for age significant at the 0.001% level and for SBP at the 0.01% level]. Multiple regression analysis including potential determinants of PWV (age, MBP, DBP, SBP, height, weight, and sex) was performed. MBP was a significant determinant of all PWV except PWV_{cr} in the diabetic group.

Expression of results as a ratio involving predominantly nonelastic to elastic arterial segments improved the relationship with age (Fig. 2). In the nondiabetic group the absolute correlation with age tended to improve from 0.483 for PWV_{cf} to 0.594 when the ratio of PWV_{cr} to PWV_{cf} was considered (P = 0.064 for the difference). When PWV_{fin} was used in the numerator of the ratio, correlation with age also tended to improve in relation to the original parameter (nondiabetic subjects 0.483 to 0.571 [P = 0.145 for the difference]; 0.116 to 0.235 [P = 0.156 for the difference] for the diabetic group).

Significant differences existed in the rate of aging (β, slope of line) of the aortic segment (PWV_{cf}) compared with the carotid radial (PWV_{cr}) segment in nondiabetic subjects (slope = 0.12 vs. −0.02 ms^{-1}/year, respectively; $P < 0.01$). The changes for year of age for the nondiabetic group were −0.011 (PWV_{cr}-to-PWV_{cf}, r^2 = 0.35) and −0.0053 (PWV_{fin}-to-PWV_{cf}, r^2 = 0.33), both significant at the 0.001% level, whereas in the diabetic group the PWV_{fin}-to-PWV_{cf} slope was −0.0024 (r^2 = 0.05, P = 0.13) and PWV_{cr}-to-PWV_{cf} slope was −0.003 (r^2 = 0.002, P = 0.30).

Correction of the ratios for measured SBP, DBP, and MBP did not alter nondiabetes associations, but the association between PWV_{fin}/PWV_{cf} and age in diabetes was attenuated (r = 0.24, P = 0.10). Multivariate analysis on age and SBP with the calculated ratios as the dependant variable was performed. The ratios were associated with age and not SBP. In nondiabetic subjects PWV_{cr}/PWV_{cf} = 1.704 − 0.011(age) − 0.000(SBP), r^2 = 0.35, and the coefficient for age was significant at the 0.001% level; and PWV_{fin}/PWV_{cf} = 0.844 − 0.005(age) − 0.001(SBP), r^2 = 0.36, and the coefficient for age was significant at the 0.001% level.

CONCLUSIONS — This study specifically investigates the relationship between arterial mechanical properties and aging in predominantly elastic compared with predominantly muscular arteries. In this context a significant finding is the apparent loss of the normal age-associated deterioration in any of the indices in the diabetic group. This is likely related to the fact that even though the diabetic subjects were on average younger, they had a higher BP and their mean values of PWV were higher in all segments than in nondiabetic subjects, suggesting that in the diabetic group age changes had occurred at an accelerated rate at an earlier age and had perhaps reached a functional plateau. Biologically, the diabetic group (mean chronological age 61 years) seems to have reached an "arterial" age approximating 75 years in those without diabetes. This is consistent with a relative lack of further deterioration from the elderly to very elderly and also consistent with reports suggesting that diabetic arteries stiffen earlier (14,15) and the fact that earlier on-

Table 3—*Univariate relation between PWV, PWV ratios, and blood pressure*

	n	DBP	MBP	SBP
Nondiabetic subjects				
PWV_{cf}	106			
Correlation		0.032	0.204	0.336
Significance (two-tailed)		0.743	0.036	0.000
Slope		0.009	0.044	0.043
PWV_{cr}	105			
Correlation		0.255	0.31	0.318
Significance (two-tailed)		0.009	0.001	0.001
Slope		0.046	0.044	0.028
PWV_{fin}	66			
Correlation		0.085	0.196	0.273
Significance (two-tailed)		0.498	0.115	0.027
Slope		0.005	0.008	0.007
PWV_{cr}-to-PWV_{cf}	104			
Correlation		0.155	0.02	−0.113
Significance (two-tailed)		0.116	0.841	0.251
Slope		0.003	0.000	−0.001
PWV_{fin}-to-PWV_{cf}	65			
Correlation		−0.088	−0.211	−0.296
Significance (two-tailed)		0.485	0.092	0.017
Slope		−0.001	−0.001	−0.001
Diabetic subjects				
PWV_{cf}	53			
Correlation		0.259	0.385	0.426
Significance (two-tailed)		0.061	0.004	0.002
Slope		0.062	0.08	0.054
PWV_{cr}	53			
Correlation		0.19	0.194	0.156
Significance (two-tailed)		0.173	0.165	0.265
Slope		0.029	0.024	0.011
PWV_{fin}	46			
Correlation		0.222	0.339	0.377
Significance (two-tailed)		0.139	0.021	0.01
Slope		0.011	0.014	0.009
PWV_{cr}-to-PWV_{cf}	50			
Correlation		−0.165	−0.26	−0.303
Significance (two-tailed)		0.251	0.068	0.033
Slope		−0.003	−0.004	−0.003
PWV_{fin}-to-PWV_{cf}	43			
Correlation		−0.232	−0.295	−0.297
Significance (two-tailed)		0.135	0.055	0.053
Slope		−0.002	−0.002	−0.001

set of clinical arterial disease in diabetes is well known.

Our findings also confirm the known difference in age-related change between elastic and muscular arteries (10,16). Our nondiabetic subject group showed a nonsignificant and small decrease in PWV with age in the carotid to radial segment (Table 2), possibly associated with a decrease in arterial stiffness. Conversely, the predominantly elastic aortic artery demonstrated a considerable age-related increase in PWV. This is consistent with previously reported changes and the location of clinically related arterial disease. CAC predominantly represents the buffering capacity of the proximal aorta. The arterial segment represented by CAC is largely precluded from involvement in PWV_{cf} assessment, as the time taken for the pressure pulse to reach the femoral artery is long, and the time taken to propagate to the transduction point at the carotid artery corresponds to passage of the aortic pressure pulse around the aortic arch. There was no statistically significant age-associated changes in CAC in our study group. However, despite their relative youth, we did demonstrate the expected lower CAC in those with diabetes compared with those without diabetes (17).

Change in specific arterial mechanical properties has been shown to bear a closer relation to chronological age than many other parameters, such as graying of hair, skin elasticity, etc., that are currently used (18). In this context it has been proposed that the assessment of "biological" as opposed to "chronological" age of an individual's artery may be of use in the management or prevention of arterial disease. Our results suggest that use of a ratio incorporating the differences between age effects on elastic and muscular arteries may be a useful means of improving the age association of arterial change in nondiabetic subjects and thus a means of improving the accuracy of assessment of arterial health. Our results further suggest that if a ratio is to be used, then either PWV_{cr} or PWV_{fin} may be used as the numerator in nondiabetic subjects. For diabetic subjects, however, the numerator should be PWV_{fin}. This is most likely due to the segment represented by PWV_{fin}, including small arteries such as those characteristically affected by diabetes.

There were apparent differences in the pressure dependence of PWV in the arterial segments studied between groups, with the effect of pressure on PWV_{cr} seemingly less in the diabetic group. One potential explanation for this could be that in this group intrinsic stiffening changes (structural or functional) had occurred to such an extent that further pressure dependence was irrelevant. However, this did not apply to PWV_{fin} and PWV_{cf}. In the PWV ratios calculated here pressure was not a significant determinant, and this further suggests that a ratio of muscular to elastic artery PWV may be a useful parameter across individuals.

Limitations of the study. There were differences in the baseline characteristics of the diabetic and nondiabetic groups. This is not a significant drawback in the current study because the aim was not to compare absolute parameters between groups but to look at relationships within groups. Nevertheless, the results demonstrate why there is much controversy re-

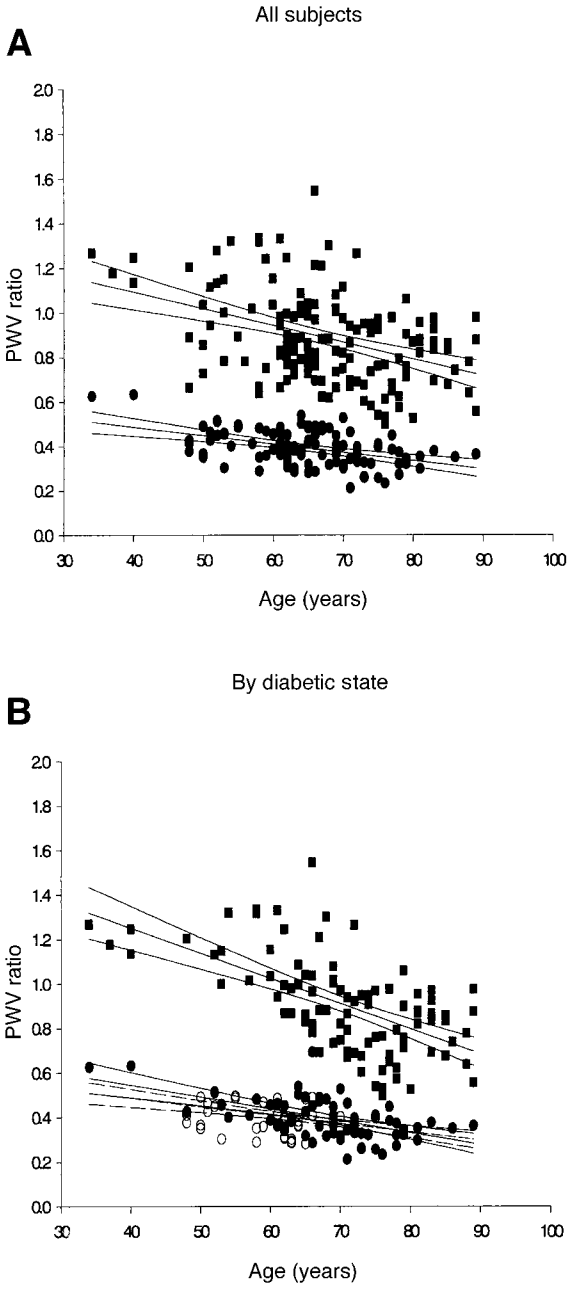

Figure 2—*PWV ratios (PWV_{cr}-to-PWV_{cf} and PWV_{fin}-to-PWV_{cf}) vs. age for all subjects* (A) *and by diabetes status* (B). A: ■, *PWV_{cr}-to-PWV_{cf}*; ●, *PWV_{fin}-to-PWV_{cf}*. B: ■, *PWV_{cr}-to-PWV_{cf} for nondiabetic subjects;* ●, *PWV_{fin}-to-PWV_{cf} for nondiabetic subjects;* ○, *PWV_{fin}-to-PWV_{cf} for diabetic subjects.*

garding the effects of diabetes on arterial compliance, positive deleterious results arising from studies in younger persons, and negative studies in older subjects in which the normal control subjects also have impaired compliance (11,18,19). All arterial mechanical properties vary with blood pressure level. As expected, all measures of BP in this study increased with age. This could have a confounding effect on our measurements of age changes in arterial properties. We do not feel that this is a significant influence, however, as conclusions were not altered by adjustment for DBP, SBP, or MBP.

In addition, the method used for measuring PWV also has limitations. The distance traveled by the pulse wave is measured on the surface of the body. The vessels in the human body do not travel in a straight line, therefore possibly confounding the measurements. The PWV_{fin}, which is a time interval measurement, has a latent period due to intraventricular activation time. This may vary in different people and may also be affected by diabetes. Diabetes affects small vessels, thus this may be a confounder in measuring PWV_{fin}.

In conclusion, we have shown significant differences in the rate of age-related deterioration in elastic arteries of nondiabetic compared with diabetic arteries. Further, we have shown that an improvement in the assessment of age-related change in elastic arteries may be obtained by the use of a ratio measure incorporating values obtained from assessment of elastic and muscular arteries separately.

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