Changes in Arterial Stiffness and Wave Reflection With Advancing Age in Healthy Men and Women

The Framingham Heart Study

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Abstract—With advancing age, arterial stiffness and wave reflections increase and elevate systolic and pulse pressures. An elevated central pulse pressure is generally ascribed to increased wave reflection and portends an unfavorable prognosis. Using arterial tonometry, we evaluated central (carotid-femoral) and peripheral (carotid-brachial) pulse wave velocity, amplitudes of forward and reflected pressure waves, and augmentation index in 188 men and 333 women in the Framingham Heart Study offspring cohort who were free of clinical cardiovascular disease, hypertension, diabetes, smoking within the past 12 months, dyslipidemia, and obesity. In multivariable linear regression models, advancing age was the predominant correlate of higher carotid-femoral pulse wave velocity; other correlates were higher mean arterial pressure, heart rate, and triglycerides and walk test before tonometry (model $R^2=0.512$, $P<0.001$). A similar model was obtained for carotid-brachial pulse wave velocity (model $R^2=0.227$, $P<0.001$), although the increase with advancing age was smaller. Owing to different relations of age to central and peripheral stiffness measures, carotid-femoral pulse wave velocity was lower than carotid-brachial pulse wave velocity before age 50 years but exceeded it thereafter, leading to reversal of the normal central-to-peripheral arterial stiffness gradient. In this healthy cohort with a minimal burden of cardiovascular disease risk factors, an age-related increase in aortic stiffness, as compared with peripheral arterial stiffness, was associated with increasing forward wave amplitude and pulse pressure and reversal of the arterial stiffness gradient. This phenomenon may facilitate forward transmission of potentially deleterious pressure pulsations into the periphery. **(*Hypertension*. 2004;43:1239-1245.)**

Key Words: aging ■ aorta ■ arteries ■ arteriosclerosis ■ elasticity ■ elderly ■ vasculature

There is a growing awareness that abnormal large artery function plays an important role in the pathogenesis of cardiovascular disease. Increased arterial stiffness, with an associated increase in the amplitudes of the forward and reflected pressure waves, is a major determinant of increased systolic and pulse pressure with advancing age. Increased levels of pulse pressure, an indirect measure of arterial stiffness, and carotid-femoral pulse wave velocity (CFPWV), a more direct measure of stiffness, are associated with adverse clinical events.[1–6] Arterial stiffening is associated with a number of known cardiovascular disease risk factors, raising the possibility that increased arterial stiffness may be a surrogate for advanced atherosclerotic vascular disease. However, prior studies have suggested that aortic stiffening can occur in the absence of atherosclerosis.[7,8] Therefore, one goal of this study was to determine the extent of arterial stiffening in central and peripheral arteries with advancing age in a middle-aged to elderly community-based sample with a minimal burden of risk factors for cardiovascular disease.

Pressure wave reflection in the arterial system serves 2 beneficial purposes. When normally timed, the reflected wave returns to the central aorta in diastole and therefore enhances diastolic perfusion pressure in the coronary circulation.[9] Partial wave reflection also returns a portion of the pulsatile energy content of the wave form to the central aorta where it is dissipated by viscous damping. Thus, wave reflection limits transmission of pulsatile energy into the periphery where it might otherwise damage the microcirculation.[10] Loss of this apparently protective function of wave reflection could contribute to the pathogenesis of a growing spectrum of cardiovascular and noncardiovascular accompaniments of aging that share a potential microvascular etiology,[11] including white matter lesions of the brain[12] and renal dysfunction.[13,14]

In the normal arterial system, there is a steep gradient of increasing arterial stiffness moving outward from the heart. In a young adult, pulse wave velocity (PWV), a close correlate of arterial wall stiffness, is only 4 to 6 m/s in the highly

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compliant proximal aorta and increases to 8 to 10 m/s in the stiffer peripheral muscular arteries. This progressive increase in regional arterial stiffness, together with branching and narrowing of the lumen, creates an impedance mismatch and leads to a partial reflection of the advancing pressure wave.[15,16] Prior studies have shown that central arterial stiffness increases to a far greater extent than peripheral arterial stiffness with advancing age.[17–19] As a result, aortic stiffness may equal or exceed peripheral arterial stiffness in the elderly. This reversal of the normal arterial stiffness gradient may diminish wave reflections and therefore increase transmission of pulsatile energy into the periphery and microcirculation.

To test these hypotheses, we designed the present study to evaluate changes in central and peripheral arterial stiffness and wave reflection with advancing age in a healthy subset of the community-based Framingham Heart Study.

Methods

Study Participants

The study design for the Framingham Offspring Study has been described elsewhere.[20] Arterial tonometry was performed routinely in participants undergoing their seventh examination cycle (1998–2001). The Boston Medical Center Institutional Review Board approved the protocol and each participant gave written informed consent. There were 2640 individuals with tonometry data (75% of participants attending the clinic examination). To generate a healthy sample, participants were excluded for the following reasons: hypertension (defined as systolic blood pressure [SBP] ≥140 mm Hg, diastolic blood pressure [DBP] ≥90 mm Hg, or drug treatment for hypertension, n=1233), diabetes (defined as a fasting blood glucose ≥126 mg/dL or treatment with insulin or an oral hypoglycemic agent, n=359), treatment for dyslipidemia (n=548), cardiovascular disease (coronary heart disease, congestive heart failure, stroke, transient ischemic attack, or intermittent claudication, n=366), current smoking (defined as smoking within the 12 months before the index examination, n=354), or obesity (defined as a body mass index [BMI] ≥30 kg/m^2, n=784). Of the remaining 667 eligible individuals, optimal tonometry at all 4 pulse sites (brachial, radial, femora,l and carotid) and results of a submaximal walk test were available in 188 men and 333 women.

Noninvasive Hemodynamic Data Acquisition

Participants were studied in the supine position after approximately 5 minutes of rest. Supine brachial SBP and DBP were obtained using an oscillometric device. Arterial tonometry with simultaneous ECG was obtained from brachial, radial, femoral, and carotid arteries using a commercially available tonometer (SPT-301, Millar Instruments, Houston, Tex). Transit distances were assessed by body surface measurements from the suprasternal notch to each pulse-recording site. Tonometry and ECG data were digitized during the primary acquisition (1000 Hz), transferred to CD-ROMs, and shipped to the core laboratory (Cardiovascular Engineering, Inc, Holliston, Mass) for analysis blinded to all clinical data.

Tonometry Data Analysis

Tonometry waveforms were signal-averaged using the ECG R-wave as a fiducial point.[21] Average systolic and diastolic cuff pressures were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were then used to calibrate carotid, radial, and femoral pressure tracings.[22] Calibrated carotid pressure was used as a surrogate for central pressure.[22] Carotid-brachial pulse wave velocity (CBPWV) and CFPWV were calculated from tonometry waveforms and body surface measurements as previously described.[23] Systolic ejection period (SEP) was measured from the foot of the carotid pressure waveform to the dicrotic notch (Figure 1). Reflected wave transit time (RWTT) was measured from the foot of the carotid pressure waveform to the first inflection point, which corresponds to the foot of the global reflected pressure wave (Figure 1).[24] The effective reflecting distance (ERD) was calculated from RWTT and CFPWV: ERD=(RWTT×CFPWV)/2.[24] Effective reflecting distance calculated in this manner correlates well with values obtained from impedance spectra.[9] Augmentation index was calculated as previously described.[24] The central forward wave amplitude was defined as the difference between pressure at the waveform foot and pressure at the first systolic inflection point or peak of the carotid pressure waveform (Figure 1). Reflected wave pressure was defined as the difference between central systolic pressure and pressure at the forward wave peak (Figure 1).

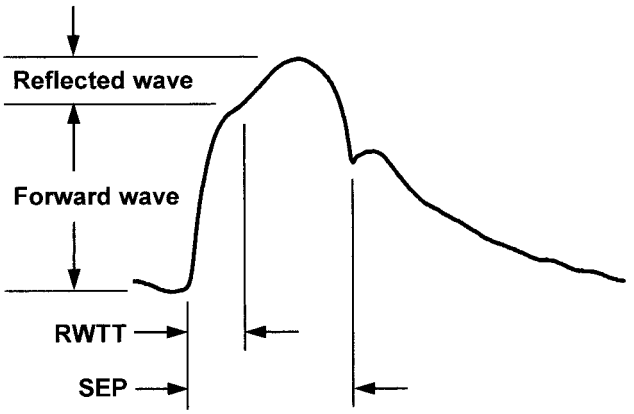

Figure 1. Carotid pressure landmarks. RWTT was identified by the first occurrence of an inflection point on the carotid pressure waveform. If the inflection point occurred before peak pressure (an augmented waveform), pressure at the inflection point minus foot pressure was the forward wave pressure and systolic pressure minus pressure at the inflection point was the reflected wave pressure. If the inflection point occurred after peak pressure (no augmentation), reflected wave pressure was zero and systolic pressure minus pressure at the foot was forward wave pressure. SEP was measured from the foot of the waveform to the dicrotic notch.

TABLE 1. Characteristics of Subjects

Variable	Men (N=188)	Women (N=333)
Age, years	56±9	57±8
Height, in	70±3	64±2
Weight, lbs	181±21	140±17
Brachial systolic pressure, mm Hg	118±11	111±11
Brachial diastolic pressure, mm Hg	73±8	64±9
Mean arterial pressure, mm Hg	91±8	84±9
Brachial pulse pressure, mm Hg	46±9	47±11
Heart rate, bpm	60±9	63±9
Body mass index, kg/m^2	26±2	24±3
Ratio of total/HDL cholesterol, −	4.2±1.2	3.2±1.1
Triglycerides, mg/dL	117±77	101±55
Fasting glucose, mg/dL	97±9	92±8
SSN−brachial distance, cm	45.7±2.2	41.7±1.9
SSN−radial distance, cm	72.2±3.4	65.3±2.9
SSN−femoral distance, cm	57.5±3.5	52.7±2.6
SSN−carotid distance, cm	9.6±1.1	8.8±1.0

SSN indicates suprasternal notch.

TABLE 2. Tonometry Variables

Variable	Men (N=188)	Women (N=333)
Central systolic pressure, mm Hg	115±12	109±14
Central pulse pressure, mm Hg	42±10	45±12
Reflected wave transit time, ms	138±28	124±28
Time to peak pressure, ms	201±53	210±29
Systolic ejection period, ms	312±23	320±22
Augmentation index, %	9±12	17±10
Forward pressure wave*, mm Hg	36±8	36±10
Reflected pressure wave, mm Hg	4.8±4.8	7.9±5.6
Carotid-femoral PWV, m/s	8.7±2.0	8.2±1.9
Carotid-brachial PWV, m/s	9.3±1.5	8.4±1.6
Carotid-radial PWV, m/s	10.3±1.3	9.7±1.4
Effective reflection distance, cm	59±15	50±16

*Forward pressure peak−foot pressure.

We evaluated analysis reproducibility of key tonometry measures in a random sample of 50 cases that were blindly reanalyzed by a second observer. Correlation coefficients for key variables were: CFPWV, $r=0.972$; RWTT, $r=0.968$; augmentation index, $r=0.997$; and SEP, $r=0.999$.

Statistical Analysis

Baseline characteristics and tonometry variables were tabulated separately for men and women. Correlations between tonometry variables and blood pressure, heart rate, anthropometric and metabolic variables were calculated. Multivariable correlates[25] of tonometry variables were assessed using sex-pooled stepwise regression analysis that always included terms for sex, age, and age-squared. Regression was performed using the SAS REG procedure with a $P\leq0.10$ inclusion criterion.[26] For age and mean arterial pressure (MAP), linear and quadratic terms were used together as a paired variable to evaluate potential nonlinearity in these relations. The quadratic terms were centered to minimize collinearity. Participants also underwent a submaximal walk test either before or after the tonometry evaluation. A walk test status variable (before versus after tonometry) was also offered as a covariate. Values are presented as mean±SD except as noted. There was no adjustment for multiple testing. A 2-sided $P<0.05$ was considered significant.

Results

Characteristics of the study sample and summary statistics for tonometry variables are presented in Tables 1 and 2, respectively. Correlations between blood pressure components, heart rate, and key tonometry variables are presented in Table 3. Forward pressure wave amplitude, CFPWV, and reflected wave pressure were directly related to brachial pulse pressure. In contrast, peripheral arterial stiffness, as assessed by CB-PWV, was not correlated with brachial pulse pressure but was correlated with SBP, DBP, and MAP. Reflected wave pressure, augmentation index, and CFPWV were moderately correlated with heart rate, although the pattern of association was discordant. Higher heart rate was associated with increased CFPWV and with lower reflected wave pressure and augmentation index (Table 3).

Correlations of key tonometry variables with anthropometric (height, weight, and BMI) and metabolic (total/HDL cholesterol ratio, triglycerides, and glucose) variables were also assessed. Despite exclusion of individuals with diabetes, hyperglycemia, or treated dyslipidemia, CFPWV was related to total/HDL cholesterol ratio ($r=0.242$ in women, $r=0.126$ in men), triglycerides ($r=0.244$ in women, $r=0.260$ in men), and fasting glucose ($r=0.172$ in women, $r=0.204$ in men). All values $P<0.05$ except total/HDL cholesterol ratio in men.

We performed stepwise regression analyses with key tonometry variables as dependent variables and with age, age-squared, sex, heart rate, MAP, MAP-squared, height, weight, body mass index, total/HDL cholesterol ratio, triglycerides, glucose, and walk test timing as potential covariates (Table 4). There was a strong, nonlinear increase in CFPWV with advancing age, as indicated by the significant age and age-squared terms (Table 4). Higher MAP, heart rate and triglycerides, and walk test before tonometry were associated with higher CFPWV. The model for CBPWV was similar, although the increase in CBPWV with age was markedly attenuated (Table 4). Forward wave amplitude was related to increasing age and MAP and was higher in women. Reflected wave pressure was higher in women than men, increased with age and MAP, and decreased with increasing heart rate and

TABLE 3. Hemodynamic Correlates of Tonometry Variables

		Correlation Values*				
Variable	Gender	SBP	DBP	Pulse Pressure	MAP	Heart Rate
Carotid-femoral PWV, m/s	Men	0.441	0.262	0.300	0.371	0.299
	Women	0.398	0.129	0.322	0.276	0.226
Carotid-brachial PWV, m/s	Men	0.207	0.330	–0.036	0.318	0.128
	Women	0.241	0.341	–0.037	0.341	0.166
Forward pressure wave, mm Hg	Men	0.576	–0.224	0.874	0.225	–0.069
	Women	0.577	–0.279	0.876	0.195	0.079
Reflected pressure wave, mm Hg	Men	0.403	0.110	0.383	0.340	–0.295
	Women	0.437	0.046	0.438	0.314	–0.213
Augmentation index, %	Men	0.308	0.242	0.159	0.360	–0.323
	Women	0.213	0.157	0.095	0.240	–0.275

*Correlations with an absolute value>0.14 in men and>0.10 in women are significant at the $P<0.05$ level.

TABLE 4. Stepwise Regression Models

Variable	Estimate per SD	Model R^2	*P*
Carotid-femoral PWV, m/s			
Age	1.04	—	<0.001
Age-squared	0.32	—	<0.001
Sex, female	–0.20	—	0.165
MAP	0.59	0.458	<0.001
MAP-squared	0.09	0.458	0.154
Heart rate	0.32	0.490	<0.001
Triglycerides	0.24	0.503	<0.001
Walk test before	0.37	0.512	0.003
Carotid-brachial PWV, m/s			
Age	0.30	—	<0.001
Age-squared	0.00	—	0.982
Sex, female	–0.57	—	<0.001
MAP	0.53	0.208	<0.001
MAP-squared	–0.06	0.208	0.370
Heart rate	0.13	0.217	0.049
Walk test before	0.24	0.222	0.066
Triglycerides	0.12	0.227	0.075
Forward pressure wave, mm Hg			
Age	2.32	—	<0.001
Age-squared	2.06	—	<0.001
Sex, female	1.88	—	0.021
MAP	2.35	0.178	<0.001
MAP-squared	–0.22	0.178	0.546
Reflected pressure wave, mm Hg			
Age	0.69	—	0.001
Age-squared	–0.39	—	0.067
Sex, female	3.29	—	<0.001
MAP	2.12	0.199	<0.001
MAP-squared	0.19	0.199	0.356
Heart rate	–1.60	0.276	<0.001
Height	–1.13	0.294	<0.001
Walk test before	–0.75	0.298	0.071
Augmentation index, %			
Age	0.93	—	0.031
Age-squared	–1.74	—	<0.001
Sex, female	7.14	—	<0.001
Heart rate	–3.68	0.233	<0.001
MAP	3.70	0.319	<0.001
MAP-squared	0.54	0.319	0.190
Height	–2.83	0.345	<0.001

Standard deviations (SD) for covariates are age=8.5 y, age-squared=98.7 y^2, heart rate=9.3 min^{-1}, height=3.8 in, MAP=9.6 mm Hg, MAP-squared=128.4 mm Hg^2 and triglycerides=64.1 mg/dL.

height. The model for augmentation index resembled the model for reflected wave pressure although there was a highly significant age-squared term indicating a convex upward relation (Table 4).

The relations of age to arterial stiffness measures in this healthy cohort are presented in Figures 2 and 3. CFPWV

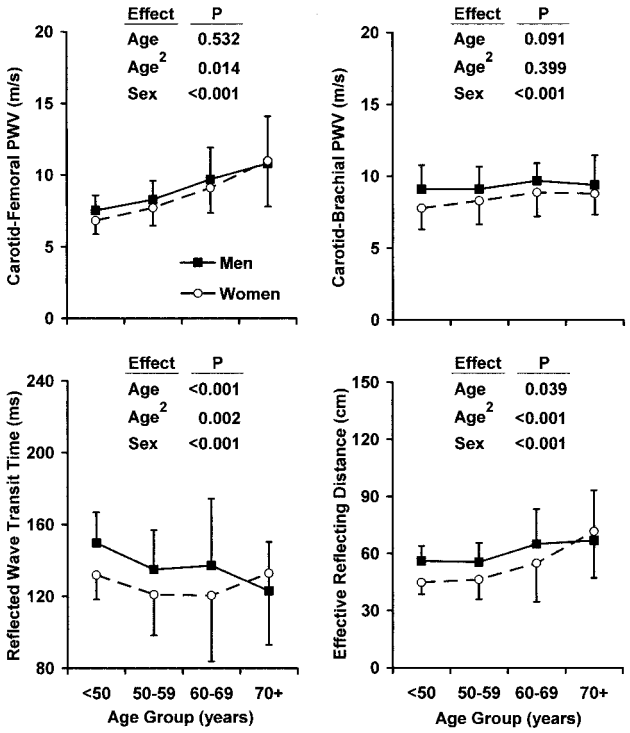

Figure 2. Means of regional pulse wave velocities and reflected wave variables by sex and decade of age. Carotid-femoral PWV increased substantially with advancing age (age² term), whereas an insignificant increase in carotid-brachial PWV was found in these unadjusted analyses. As a result, carotid-femoral PWV exceeded carotid-brachial PWV in older participants. Aortic stiffening was accompanied by a proportional decrease in reflected wave transit time in younger but not older groups; therefore, distance to the effective reflecting site increased in older individuals. Numbers per group (Men/Women): <50 years, n=43/52; 50 to 59 years, n=74/172; 60 to 69 years, n=57/82; and 70+ years, n=14/27.

increased with advancing age, whereas CBPWV did not differ in these unadjusted analyses (Figure 2). The initial increase in CFPWV with age (<60 years), at a time when CFPWV was less than CBPWV, was accompanied by a reciprocal decrease in RWTT, no change in the location of major reflecting sites, as assessed by ERD (Figure 2), and an increase in augmentation index (Figure 3). However, after age 60 years, CFPWV equaled and then exceeded CBPWV. Further reductions in RWTT were attenuated and reflecting sites shifted to more distal locations (increased ERD, Figure 2). Forward wave amplitude continued to increase, whereas the relative amplitude of the reflected wave (augmentation index) reached a maximum (in men) or fell (in women), even though reflected wave timing remained premature (Figure 3).

Discussion

In a healthy sample with no evidence of cardiovascular disease and a low burden of risk factors, we found a marked age-related increase in aortic stiffness, as assessed by CF-PWV, with little change in peripheral arterial stiffness, as assessed by CBPWV. In contrast, reflected wave amplitude changed minimally with advancing age, despite a steady increase in forward wave amplitude, suggesting that increases in central aortic stiffness and forward wave amplitude, rather

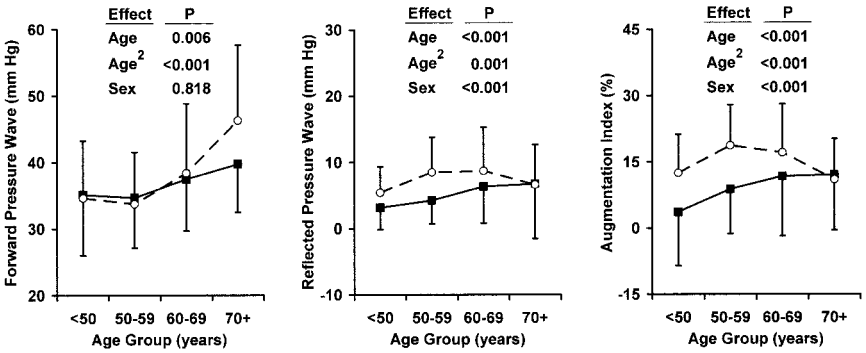

Figure 3. Means of carotid waveform variables by sex and decade of age. Forward pressure wave amplitude increased dramatically whereas reflected pressure wave amplitude and augmentation index increased initially and then fell.

than reflected wave amplitude, are the primary mechanisms for increased central and peripheral systolic and pulse pressure with advancing age in healthy adults. Although there were modest relations of CFPWV with levels of glucose, lipids, and MAP in this healthy cohort, age remained by far the strongest correlate of CFPWV and forward wave amplitude in multivariable regression analyses.

As in prior studies,[17,18] we found regional heterogeneity in arterial stiffening with advancing age in our cohort. The marked increase in aortic stiffness with age with little change in peripheral arterial stiffness resulted in a reversal of the gradient of arterial stiffness from the youthful pattern of a compliant proximal aorta, which was evident in individuals aged <50 years, to a pattern of greater aortic stiffness in older participants. This transition to higher central as compared with peripheral arterial stiffness was marked by a turning point in the absolute and relative amplitude of the reflected pressure wave. These changes in wave reflection with advancing age are consistent with the hypothesis that a marked increase in CFPWV with little change in CBPWV leads to impedance matching between central aorta and proximal muscular arteries, which reduces proximal wave reflection and shifts reflecting sites distally.

These data provide new insights into the variable mechanisms of age-related loss of peripheral pressure amplification, which has been shown to portend an adverse clinical outcome.[27] In young adults with a reflected pressure wave arriving centrally during diastole, pulse pressure is substantially higher in the periphery as compared with the central aorta.[28] This amplification of the pressure waveform as it propagates distally represents the dual effects of progressive stiffening of vessels with increasing distance from the heart and relatively earlier timing of local reflections as the advancing wave approaches reflecting sites.[15] In middle-age, increasing pulse wave velocity leads to premature return of the reflected pressure wave to the central aorta during systole, which augments central systolic and pulse pressure and reduces peripheral amplification.[29] Finally, in the elderly, we have shown that central arterial stiffness exceeds peripheral arterial stiffness. This loss of the normal arterial stiffness gradient may reduce amplification and reflection and increase transmission of a larger potentially harmful forward pressure wave into the microcirculation.

Prior studies evaluated changes in pressure waveform morphology and pulse wave velocity with advancing age and demonstrated that central aortic stiffness increases with advancing age even in relatively healthy individuals.[7,8,10,29,30] The present study, however, is the first to describe the changes in wave reflection and pulse waveform morphology that follow from these differential changes in regional arterial properties. It is important to note that we measured arterial stiffness in the arms but not in the legs. However, prior studies have shown a similar pattern of minimal stiffening with advancing age in the legs.[17,18] We modeled wave reflections as though they arose from a single "effective" reflecting site. Actually, there are innumerable reflecting sites that produce a summated reflected wave that appears to arise from a single "effective" reflecting site (Figure 1).

We found several additional correlates of wave reflection, including a prominent sex difference and relations with height and heart rate, which have been observed in prior studies.[31–34] The reductions in reflected wave amplitude and augmentation index with increasing heart rate in the multivariable models are consistent with a shorter SEP at higher heart rate resulting in less overlap between forward and reflected waves. Women had larger reflected waves than men, in part due to shorter height and closer physical proximity between heart and reflecting sites. However, height was not sufficient to fully explain higher reflected wave pressure in women in multivariable analyses (Table 4), which is consistent with findings of a prior study of elderly men and women who were matched for height.[33] Thus, there are unexplained differences in arterial structure or function between men and women that lead to increased wave reflection in women.

We found significant correlations between heart rate and several tonometry variables, including positive relationships with CFPWV and CBPWV and negative relationships with reflected wave pressure and augmentation index as described above. Increased heart rate may be an indicator of increased sympathetic tone, which may increase the stiffness of large arteries directly.[35] Alternatively, increased large artery stiffness is associated with reduced baroreceptor sensitivity, which could alter sympathetic tone and heart rate.[36,37] Chronically elevated heart rate may increase large artery stiffness by accelerating elastin breakdown in the arterial wall[38] or because wall stiffness is modestly frequency dependent.[39] In paced animal models, increased heart rate was shown to increase stiffness of large elastic arteries while having a variable effect on muscular arteries.[40,41] We also found that the heart rate-PWV relationship was steeper for CFPWV, which encompasses a substantial segment of elastic aorta, as

compared with CBPWV, which encompasses predominantly muscular arteries.[42] Although the mechanism remains incompletely defined, there is clearly a modest relationship between heart rate and PWV that should be considered when interpreting PWV values.

There are limitations to our study that should be considered. To determine systolic and diastolic pressure for calibration of tonometry data, we used an oscillometric blood pressure device, which may have introduced calibration errors. However, it is important to note that many of the measures that we have reported, such as regional pulse wave velocities, timing of wave reflection, and augmentation index are independent of pressure calibration. Furthermore, the pattern of relative change in forward versus reflected wave is not affected by calibration errors because the effects on forward and reflected waves are proportional. We estimated forward wave amplitude from the carotid pressure waveform without measuring the corresponding aortic flow, which is needed to separate forward and reflected waves. To test the validity of this approach, we analyzed pressure and flow data from a previously reported cohort[43] and found that forward wave amplitude estimated from the carotid pressure waveform alone provided a robust estimate of forward wave amplitude estimated from carotid pressure and aortic flow ($n=158$, $R=0.879$, $P<0.001$).

Perspectives

We have shown that in a healthy, community-based sample of middle-aged and elderly individuals with no known cardiovascular disease and a low burden of conventional cardiovascular disease risk factors, aortic stiffness increases dramatically with advancing age. Our findings are consistent with the hypothesis that changes in central aortic stiffness and forward wave amplitude, rather than wave reflection, are responsible for most of the increase in pulse pressure in the elderly. In contrast, the stiffness of second and third generation muscular arteries increases minimally with age, leading to reversal of the normal central-to-peripheral arterial stiffness gradient, a shift of reflecting sites to more distal locations and a reduction in relative amplitude of the reflected pressure wave. Increased forward transmission of a larger forward wave may expose the peripheral small arteries and microvessels to damaging levels of pressure pulsatility and may contribute to an emerging spectrum of microvascular disorders that are common in the elderly.

Acknowledgments

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