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Age-Associated Changes in Regional Aortic Pulse Wave Velocity

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OBJECTIVES This study was designed to determine noninvasively the age-associated changes in regional mechanical properties in normals using phase-contrast magnetic resonance imaging (PC-MRI).

BACKGROUND It has been well documented that there is a progressive increase in aortic pulse wave velocity (PWV) with age. Previously, PWV has been measured at a single aortic location, or has compared arterial waves between carotid and femoral points to determine PWV.

METHODS Applanation tonometry (TONO) and in-plane PCMR was performed in 24 volunteers (12 men) ranging in age from 21 to 72 years old. The PCMRI PWV was measured in three aortic segments. As validation, TONO was performed to determine PWV between the carotid and femoral artery.

RESULTS When PCMRI PWV was averaged over the three locations, it was not different from TONO (7.9 ± 2.3 vs. 7.6 ± 2.4 m/s, respectively). When the volunteers were divided into groups of <55 and ≥ 55 years old, the younger group showed similar PWV at each aortic location. However, the older group displayed significantly increased PWV in the region spanning the ascending and proximal descending aorta compared with the mid-thoracic or abdominal segments (10.6 ± 2.5 m/s, 9.2 ± 2.8 m/s, and 7.1 ± 1.7 m/s, respectively, $p < 0.001$, analysis of variance).

CONCLUSIONS In-plane PCMRI permits determination of PWV in multiple aortic locations in a single acquisition. Progressive fragmentation of elastic fibers and alterations in the regulation of vascular tone may result in an age-related, regional increase in PWV primarily affecting the proximal aorta. (J Am Coll Cardiol 2001;38:1123–9) © 2001 by the American College of Cardiology

Two important and modifiable risk factors for cardiovascular disease are hypertension and increased left ventricular mass, and the latter remains significant even after adjusting for elevated blood pressure (1,2). Elevated blood pressure, especially of the systolic component, and increased left ventricular mass are more common with increasing age. About two-thirds of people aged 65 years and older have hypertension (3–5).

Accordingly, considerable attention has been devoted to studying age-dependent pathophysiologic contributors to these risk factors. Because aging in adulthood is associated with a loss of elasticity of the aorta and its major branches, both invasive and noninvasive methods for quantifying vascular stiffness have been explored (6–14). Though manometer-tipped catheters enable precise measures of vascular stiffness at specific regions of vessels, these approaches have limited clinical utility. Noninvasive methods include cross-sectional echocardiography, magnetic resonance imaging (MRI) and applanation tonometry (TONO). However, reported methodologies suffer from either assuming that measurements at a single vascular site (e.g., the common carotid artery) are representative of other vessels (e.g., the ascending aorta), or deriving a global measurement from averaging assessments over a large vascular bed. Proper evaluation must recognize that the aorta differs both structurally and functionally along its substantial length (15).

Phase-contrast MRI (PCMRI) can be employed to measure blood velocity accurately based on accumulated phase shifts as the blood moves through a superimposed magnetic-field gradient. Previous PCMRI studies acquired images of the aorta in cross section to measure flow (13), or at multiple locations to measure pulse wave velocity (PWV) (12). We have refined PCMRI to enable acquisition of long axis images of the entire aorta, and to permit determination of PWV between any two points along the aorta. This approach, coupled with TONO, was used in the present study to assess age-related changes in PWV at different aortic locations in healthy human subjects. The results demonstrate important regional heterogeneity of PWV that may alter our current understanding of cardiovascular aging.

METHODS

Patient population. The patient population consisted of 24 normal, normotensive volunteers (mean age 54 ± 15

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Abbreviations and Acronyms

ANOVA	=	analysis of variance
Ca1	=	calcium ionophore
ECG	=	electrocardiogram/electrocardiographic
eNOS	=	endothelial nitric oxide synthase
iNOS	=	inducible nitric oxide synthase
MRI	=	magnetic resonance imaging
NOS	=	nitric oxide synthase
PCMRI	=	phase-contrast magnetic resonance imaging
PWV	=	pulse wave velocity
ROI	=	region of interest
TONO	=	applanation tonometry
TNF-α	=	tumor necrosis factor-alpha

years, range 21 to 72 years; 12 men). Based on clinical history and echocardiography, volunteers had a <5% likelihood of cardiovascular disease using Bayesian analysis (16). Aortic cross-sectional and longitudinal magnetic resonance images confirmed the absence of detectable atherosclerotic disease in all subjects. The study protocol was approved by the Allegheny General Hospital Institutional Review Board, and all subjects provided informed consent.

PCMRI. Images were acquired with subjects in the supine position in a Siemens 1.5T MRI scanner (Siemens Medical Systems, Iselin, New Jersey). Axial localizer images were used to identify the positions of the ascending and descending aorta. Para-sagittal gradient echo images were then acquired to identify a single plane that visualized the greatest portion of ascending and descending aorta. Electrocardiographic (ECG)-gated PCMRI with in-plane phase encoding from head-to-foot was then acquired in this orientation. The PCMRI used a phase sensitivity of ±150 cm/s, slice thickness of 6 mm, time to echo of 6 ms, a repetition time of 25 ms, and a flip angle of 30°. The field of view for the parasagittal images was 300 mm × 500 mm. Noninvasive brachial artery blood pressure was recorded immediately before and after each PCMRI acquisition. Reproducibility was tested by repeat imaging of a group of five volunteers. After initial images from the PCMRI were acquired, additional images were acquired based on a different set of scout images. A third set was acquired after removing and repositioning the volunteer in the scanner.

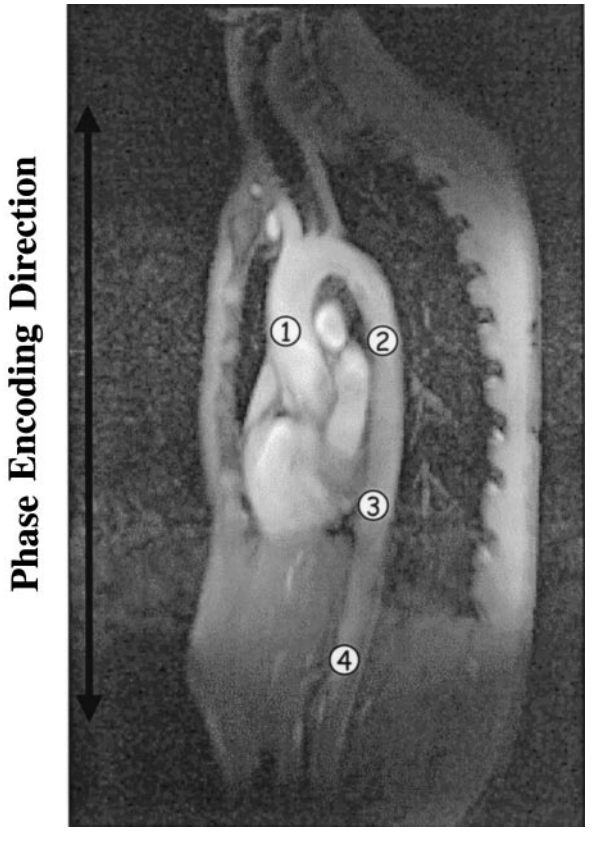

Figure 1. Magnetic resonance image showing the aorta in long axis from root through abdominal sections. Numbered regions of interest (ROIs) indicate where velocity-time curves were generated. The pulse wave velocity was determined between ROI 1–2 ("proximal"), ROI 2–3 ("mid"), and ROI 3–4 ("distal").

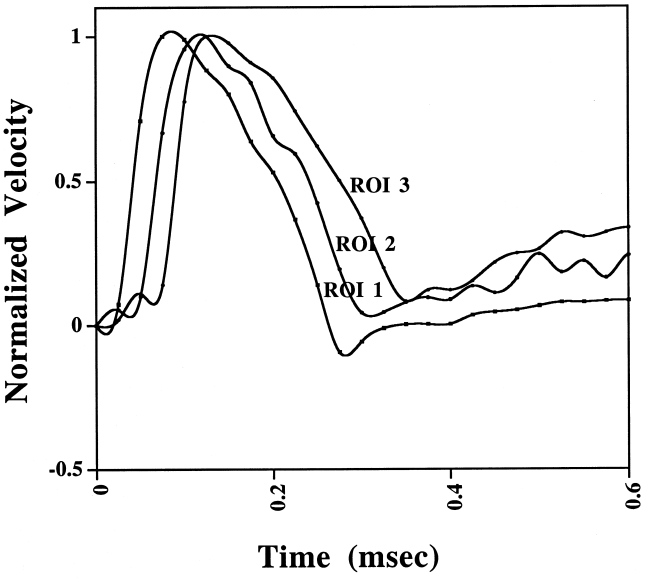

Figure 2. Example of three normalized velocity-time curves generated from three successive intraaortic regions of interest (ROIs). All curves are scaled to have the same peak velocity value. A progressive time-delay in the arrival of the velocity wave between curves 1, 2 and 3 results in a rightward shift of each curve.

Analysis of PCMRI data. Images were transferred to a SUN Ultra Sparc I workstation (Sun Microsystems, Mountain View, California). Using the magnitude images, four regions of interest (ROIs) at least 15 cm apart were positioned within the aorta. A representative example is shown in Figure 1. These four ROIs permitted calculation of PWV in three sections of the aorta. The section between ROI 1 and ROI 2 included the aortic root, arch and proximal descending aorta and is referred to as "proximal." The section between ROI 2 and ROI 3 included the proximal and mid-descending thoracic aorta and is referred to as "mid." The aorta between ROI 3 and ROI 4 included the mid-thoracic to abdominal aorta and is referred to as "distal." The ROIs were copied to the phase images, and time-velocity curves were generated for each ROI (Fig. 2).

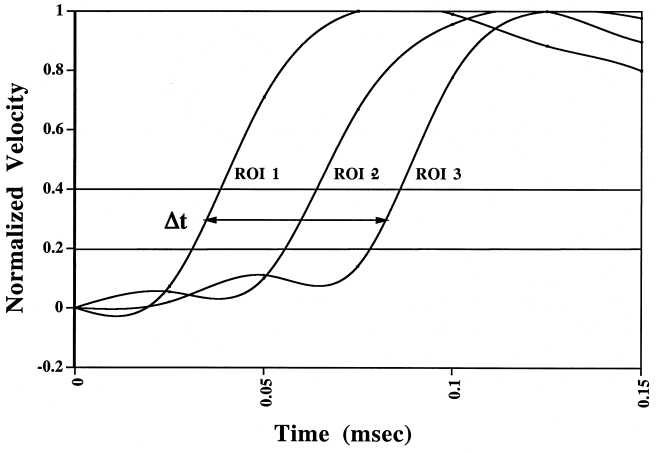

Figure 3. The location of the best cross-correlation of the upstroke portion of the velocity-time curves (with normalized velocity value between 0.2 and 0.4 on the y-axis) was used to estimate the time delay (x-axis). The time interval (Δt) is shown by the arrow. ROI = region of interest.

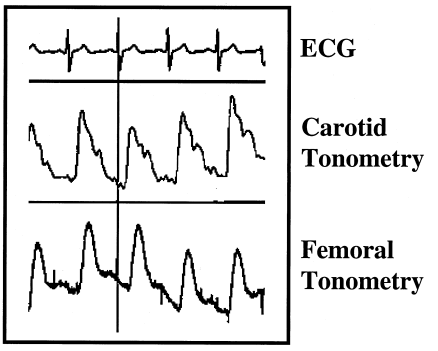

Figure 4. Simultaneous recordings of electrocardiogram (ECG), carotid and femoral tonometry. Using the ECG *r*-wave as a reference point, the delay between the carotid and femoral pressure wave permitted calculation of pulse wave velocity between two transducer points.

Pulse wave velocity was computed based on the upstroke time difference of the velocity time curves at two different regions, PWV = $\Delta x/\Delta t$, where Δx is the distance, and Δt is the time difference of initial flow acceleration between the two regions. The velocity time curve was interpolated with a spline interpolation. The upstroke velocity is approximately linear and usually contains three or more sample points. We normalized the velocity curves to individual peak velocity. The location of the best cross-correlation of two partial upstroke velocity curves (with normalized velocity value between 0.2 and 0.4) was used to estimate the time delay (Fig. 3).

Tonometry. Digitized tracings of the ECG and noninvasive arterial pulse waveforms were acquired in all subjects while in the supine position after lying recumbent for 10 min. The TONO was performed within 15 min of PCMRI. Carotid and femoral waveforms were derived from Millar SP-301 pencil-type force transducers (Millar Instruments, Houston, Texas) and recorded simultaneously with the ECG. Arterial waveforms and ECG were digitized at 250 Hz into three separate channels and stored on a laptop PC that continuously displayed pressure and ECG signals to permit optimal transducer positioning. Signals were recorded for 30 s in each subject. Blood pressure was recorded before and after each TONO measurement, and the body surface distance, measured with inelastic tape was recorded between pressure transducer locations. Reproducibility was tested in a subgroup of five volunteers using an additional 30-s acquisition of ECG and pressure waveforms during the same session.

Analysis of tonometry data. Arterial waveforms were processed with a 100-Hz low-pass filter. Ten cycles were averaged from each transducer location. When ectopic beats were encountered, three cycles prior to and after the ectopic beat were excluded from signal averaging. The TONO PWV was computed by dividing the "path length difference" (manubrium-femoral distance minus manubrium-carotid distance) by the arrival time difference between carotid and femoral waveforms as described by Vaitkevicius et al. (10). In that the origin of the pressure wave is the left ventricle, the distance traveled to the carotid transducer site is simultaneously traversed along the proximal aorta. Failure to subtract this distance in calculation of Δx would result in overestimation of PWV in the aorta. The presented PC-MRI computes PWV based on velocity data taken directly within the aorta rather than from a lumped carotid-femoral vessel segment. Using the ECG r-wave as a reference, the time difference between carotid and femoral waves was determined from the foot-to-foot delay. The "foot" was defined as the point at which a sharp systolic upstroke began in the pressure wave data (Fig. 4). Pulse wave velocity was expressed in m/s.

Statistical analysis. Results were expressed as mean ± 1 SD. Patients were grouped as being either <55 years of age or ≥55 years. Differences in baseline characteristics between groups were assessed by a two-tailed *t* test for independent sample means. The significance of differences in PWV between age groups was assessed using the *t* test for independent sample means. A two-way analysis of variance (ANOVA) was used to assess the effects of age group (<55 vs. ≥55 years) and aortic section ("proximal," "middle," and "distal") on PWV. Simple linear regression was used to determine the relationships between PWV and age, blood pressure and pulse pressure. Multiple linear regression was used to describe the relationship between PWV and age, and between systolic and pulse pressures. A two-tailed p value ≤0.05 was considered statistically significant. The coefficient of variation is the standard deviation of a distribution divided by the mean, multiplied by 100. It was used to compare the dispersions of PWV measures at different locations and in different age groups. It is expressed as a percent. The reproducibility of TONO measurements was assessed using the paired *t* test. Reproducibility of PCMRI measurements was obtained from a one-way repeated measures ANOVA.

RESULTS

The PCMRI PWV (generated from velocity-time curves) for the entire aortic length studied was 7.9 ± 2.3 m/s, which was not different from that obtained by TONO-derived pressure-time curves (7.6 ± 2.4 m/s, p = 0.380). Heart rates recorded with subjects supine were not different between MRI and TONO (72 ± 11 and 69 ± 10 beats/min, respectively, p = 0.256). The MRI regional PWV was 9.1 ± 3.0 m/s in the proximal aorta, 8.1 ± 2.8 m/s in the mid- and 7.0 ± 2.5 m/s in the distal aorta (p = 0.043), one-way ANOVA. There was a significant (p < 0.001) difference in PCMRI PWV between the two age groups (<55 years, n = 9, and ≥55 years, n = 15). Mean PCMRI PWV over the entire aortic length imaged was 6.7 ± 2.5 m/s for <55 years, versus 8.6 ± 1.9 m/s for the ≥55 group (p = 0.044). The TONO PWV age differences were similar to those measured by PCMRI with a TONO PWV of 6.3 ± 2.3 m/s in the <55 group and 8.3 ± 2.2 m/s in the ≥55 group (p = 0.059). However, after controlling for age, (two-way ANOVA) there was not a significant difference between PCMRI PWV at the proximal, mid- and distal locations (p = 0.840, two-way ANOVA). A significant interaction existed between the two main effects of age and location (p = 0.036). Thus, the difference in PWV between aortic regions was larger in those ≥55 years than in those <55 years.

Specifically, the age-associated increase in PWV was greater in the "proximal" aorta than in the "mid" or "distal" region (Fig. 5). Thus, younger individuals had similar PWV values throughout their aorta (6.2 ± 1.4, 6.1 ± 1.6 and 6.8 ± 3.7 m/s for "proximal," "mid," and "distal," respectively, p = 0.433), while the ≥55-year group had significantly increased PWV in the "proximal" (10.6 ± 2.5 m/s) compared to the "mid" (9.2 ± 2.8 m/s, p = 0.049), or "distal" region (7.1 ± 1.7 m/s, p = 0.006). The PWV was not different between the "mid" and the "distal" aorta in the ≥55-year group. The <55- and ≥55-year groups differed in the range of PWV values and the coefficient of variation of PWV values (Table 1).

Linear regression analysis showed a modest significant relationship between TONO PWV and age (r = 0.6, p = 0.007, Fig. 6). Regional MRI PWV showed the strongest relationship between age and PWV in the proximal aorta (r = 0.8, p < 0.001, Fig. 7). The MRI age–PWV relationship in the mid-descending thoracic aorta (Fig. 8) was similar to that measured by TONO (r = 0.6, p = 0.024). The MRI PWV in the distal descending aorta (Fig. 9) was not related to age (r = 0.3, p = 0.100). Both systolic pressure and pulse pressure were modestly associated with age, whereas diastolic pressure was not (r = 0.49, p = 0.038; r = 0.49, p = 0.027; and r = 0.05, p = 0.616, respectively).

Table 1. Variability of Regional Pulse Wave Velocity by Age

Location	Age Group (yrs)	Range (m/s)	Coefficient of Variation (%)
Proximal	<55	4.8–8.6	22.6
	≥55	5.8–15.0	23.6
Mid	<55	4.8–7.0	14.7
	≥55	5.3–14.7	29.6
Distal	<55	4.7–6.4	14.2
	≥55	4.7–16.0	35.8

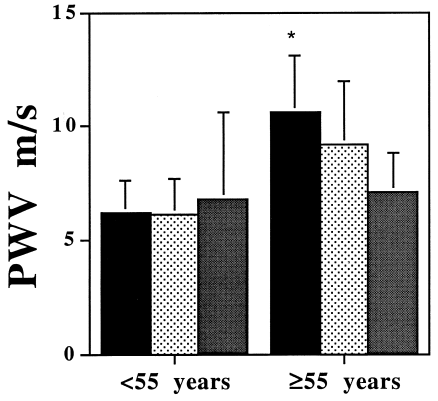

Figure 5. The pulse wave velocity (PWV) separated by age (<55 and ≥55 years) and by aortic location. Similar PWV values observed in three measured aortic locations in the <55-year-old group are contrasted by increased PWV in the "proximal" aorta in the ≥55-year-old group. **Black bars** = proximal region; **dotted bars** = midregion; **gray bars** = distal region. *p<0.005 vs. "distal" aorta in ≥55-year-old group.

Multiple linear regression comparing age and pulse pressure to PWV showed a significant effect of age (beta = 0.120, p = 0.015) but not pulse pressure in the proximal aortic region. A similar effect was shown in the mid-aortic region (beta = 0.0101, p = 0.040). Neither variable had an effect in the distal aortic region.

Using the regression equation generated for each aortic section, our data indicated that PWV in the "proximal" aorta showed a 2.7-fold increase from 21 to 72 years (4.4 vs. 12.0 m/s, respectively) compared to the mid-thoracic aorta, which displayed a 2.3-fold change (4.5 m/s at 21 years vs. 10.1 m/s at 72 years), and the distal abdominal aorta, which

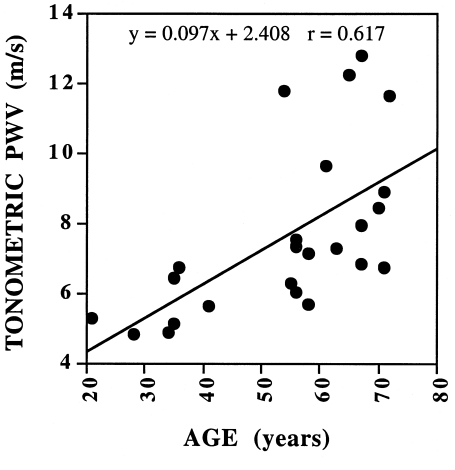

Figure 6. Relationship between tonometric pulse wave velocity (PWV) and age in 24 healthy volunteers ranging in age from 21 to 72 years. Linear regression analysis resulted in a moderate relationship (r = 0.6, p < 0.01).

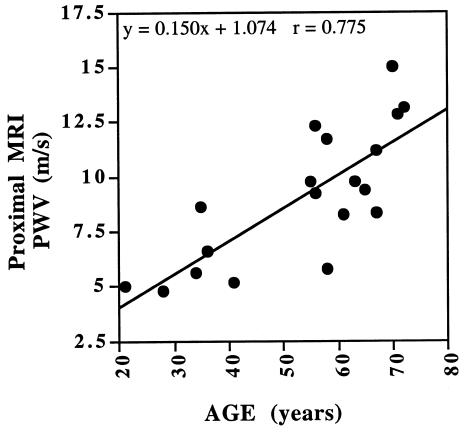

Figure 7. The magnetic resonance imaging (MRI)-derived regional pulse wave velocity (PWV) versus age in the "proximal" aorta produced the strongest linear relationship ($r = 0.8$, $p < 0.001$) between these two variables.

showed only a modest 1.6-fold change (5.1 vs. 8.0 m/s, respectively).

The mean aortic diameter (measured at the proximal portion of each segment) was 3.0 ± 0.4 cm, 2.0 ± 0.3 cm, and 1.8 ± 0.3 cm for the proximal, mid- and distal aortic segments, respectively ($p < 0.001$, ANOVA). When aortic diameters were normalized by body surface area, there was a modest linear relationship between diameter and age ($r = 0.61$, $p = 0.006$ in the proximal segment, $r = 0.64$, $p = 0.003$ in the mid-segment, and $r = 0.61$, $p = 0.005$ in the distal segment).

Reproducibility. In a group of five volunteers having repeated tonometric measurements, there was good agreement between PWV determinations (5.7 ± 0.9 vs. 5.6 ± 0.8 m/s, $p = 0.994$). In a different group of five volunteers, PCMRI-derived PWV averaged 6.5 ± 1.4 m/s, 6.4 ± 1.3 m/s, and 6.6 ± 1.9 m/s ($p = 0.565$) after initial, PCMRI after acquisition of new scout images, and after repositioning volunteers.

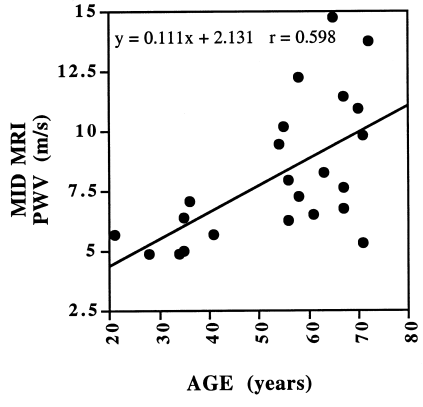

Figure 8. The magnetic resonance imaging (MRI) pulse wave velocity (PWV)–age relationship at the "mid" aorta was similar to that measured by tonometry with an $r = 0.6$, $p < 0.05$). Increasing variation in PWV values with age can be noted.

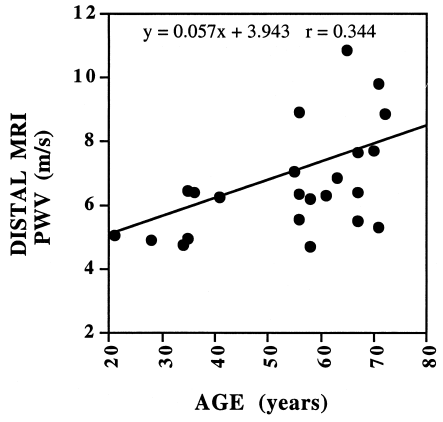

Figure 9. The pulse wave velocity (PWV) measurements by magnetic resonance imaging (MRI) in the "distal" aorta were not significantly related to age ($r = 0.3$, $p = NS$).

DISCUSSION

The aorta is not a simple conduit for blood distribution. The viscoelastic properties of the proximal aorta absorb the energy of left ventricular ejection and dampen pulsatile flow. The aorta is regionally heterogeneous. Structurally, the ratio of elastic fibers to collagen changes from 3.1:1 in the proximal ascending aorta to 2.8:1 in the mid-thoracic region to 0.8:1 in the abdominal region (15). Thus, the progressive fragmentation of elastin that occurs throughout life (17) might be expected to have a greater effect on the proximal ascending region. However, arterial stiffness may be defined by more than the structural elements within the arterial wall (18).

Factors contributing to vascular tone. Two isoforms of nitric oxide synthase (NOS) are involved in regulation of vascular tone through relaxation of arterial smooth muscle. Cernadas et al. (19) reported that in young rat aortas the inducible NOS (iNOS) was absent, while it was markedly expressed in aged rat aortas. Expression of endothelial NOS (eNOS), while present in young rat aortas, was also increased in aged aorta. Additionally, cytokines, specifically tumor necrosis factor-alpha (TNF-α) and interleukin-6, are increased in the vascular wall of aged rats (20); TNF-α reduces eNOS protein production (21); eNOS activity is inhibited by NO itself, whereas iNOS activity is resistant to inhibition by nitric oxide (NO) (22). Thus, NO in the aged arterial wall is reduced both by negative feedback of NO on constitutive eNOS activity and by way of reduced eNOS expression from increased cytokine activity. Elkouri et al. (23) demonstrated a location-dependent response to calcium ionophore (Ca1). Endothelial-dependent relaxation to Ca1 was reduced in the infrarenal aorta in a rat model of reactivity, suggesting a regional diminution of NOS activity.

Evaluation of arterial mechanical properties by MRI. The present study used PCMRI in a single para-sagittal plane to measure PWV in multiple locations in a healthy age-varied population. The MRI PWV that was pooled over all locations was similar to PWV measured by TONO

in the same subjects. The regression coefficient for pooled MRI PWV compared to age was similar to that reported by Vaitkevicius et al. (10) using tonometry in 146 highly screened healthy volunteers. They reported a regression coefficient for age versus PWV of r = 0.55 versus 0.62 and 0.57 for TONO and PCMR in the present study. Using a multisensor pressure catheter, Latham et al. (24) documented regional aortic velocities in a group of nine patients (age 42 ± 5 years) determined by catheterization to have normal coronary arteries. Pressure wave velocity was measured from the aortic root to the distal iliac artery. Wave velocity over the region evaluated in their study (24) was not significantly different between locations, ranging from 4.4 ± 0.4 m/s in the aortic root to 5.7 ± 0.4 m/s at the level of the renal arteries. This was slightly lower than observed in the <55-year group in the present study, but similarly showed no regional difference in velocity.

Because of the regional heterogeneity of the age-related increase in aortic PWV, measurements at a single location or a single measure of the entire aorta may incompletely or inaccurately describe PWV. For example, we demonstrated here that the PWV in the "proximal" aorta showed a 2.7-fold increase from 21 to 72 years compared to the mid-thoracic aorta, which displayed a 2.3-fold, and the distal abdominal aorta, which showed only a modest 1.6-fold change. The age-related increase in the proximal and mid-aortic regions are similar to TONO-derived PWV measurements by Vaitkevicius et al. (10) in well-screened normals, and Avolio et al. (9) in a rural Chinese population.

Our results show increasing variation in PWV with increasing age for both MRI and TONO methods (Figs. 6–9). Though our population had a low probability of atherosclerotic disease based on clinical history and the appearance of the aortic wall on MRI, the presence of varying degrees of subclinical disease cannot be excluded and could explain the progressive increase in PWV variability with age.

To compute PWV by TONO, the distance between transducer locations must be estimated. Increasing tortuosity along the length of the aorta with age (25) may result in an underestimation of the actual aortic path length using surface distance measurement methods. This would result in an underestimation of true PWV. Magnetic resonance imaging permits accurate determination of aortic path length from 2D or 3D images.

Using PCMRI, Groenink et al. (12) derived PWV from velocity-time curves at multiple aortic locations. Images of the aorta were acquired in cross section with separate acquisitions at each location. The MRI-derived PWV over the entire aorta averaged 3.9 m/s in a group of six young (26 ± 5 years) healthy volunteers. This is similar to the PWV predicted by the regression equation at 21 years in both the proximal and mid-region of the descending thoracic aorta (Figs. 7, 8). The method by Groenink et al. (12) differs from the present study, which acquired a single para-sagittal phase-contrast acquisition of the aorta (Fig. 2). The approach described in the present study has these advantages: First, no assumption of a hemodynamic steady-state between multiple acquisitions must be made. Second, analysis of PWV between multiple arbitrary aortic locations is possible.

Conclusions. The present study validated an in-plane phase-contrast MRI to TONO for the determination of PWV. Although PCMRI results pooled over three aortic locations were very similar to those derived from TONO, analysis of PWV at individual aortic locations disclosed significant heterogeneity. Therefore, methods that average PWV over the entire aorta or perform measurements at a single locus may be insensitive to the regional effects of the aging process on aortic function. In the present study, the proximal segment of the aorta dominated the observed relationship between increasing age and increasing vascular stiffness.

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