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The Relationship Between Vascular Wall Shear Stress and Flow-Mediated Dilation: Endothelial Function Assessed by Phase-Contrast Magnetic Resonance Angiography

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OBJECTIVES We sought: 1) to investigate the relationship between vascular wall shear stress and flow-mediated dilation (FMD) in humans, and 2) to investigate whether this relationship could explain why FMD is greater in small arteries.

BACKGROUND Arterial wall shear stress (WSS) is considered to be the primary stimulus for the endothelial-dependent FMD response. However, the relationship between WSS and FMD has not been investigated in humans. Furthermore, FMD is greater in small arteries, though the reasons for this phenomenon are unclear.

METHODS Using phase-contrast magnetic resonance angiography (PMRCA), we measured hyperemic WSS and FMD in 18 healthy volunteers. Peak systolic WSS was calculated assuming a blunted parabolic velocity profile. Diameter by PCMRA and by ultrasound was compared in nine subjects.

RESULTS Flow-mediated dilation was linearly proportional to hyperemic peak systolic WSS ($r = 0.79$, $p = 0.0001$). Flow-mediated dilation was inversely related to baseline diameter ($r = 0.62$, $p = 0.006$), but the hyperemic peak WSS stimulus was also inversely related to baseline diameter ($r = 0.47$, $p = 0.049$). Phase-contrast magnetic resonance angiography and ultrasound diameters were compared in nine subjects and correlated well ($r = 0.84$, $p < 0.0001$), but diameter by PCMRA was greater (4.1 ± 0.7 mm vs. 3.7 ± 0.5 mm, $p = 0.009$).

CONCLUSIONS Arterial FMD is linearly proportional to peak hyperemic WSS in normal subjects. Thus, the endothelial response is linearly proportional to the stimulus. Furthermore, the greater FMD response in small arteries is accounted for, at least partially, by a greater hyperemic WSS stimulus in small arteries. By allowing the calculation of vascular WSS, which is the stimulus for FMD, and by imaging a fixed arterial cross-section, thus reducing operator dependence, PCMRA enhances the assessment of vascular endothelial function. (J Am Coll Cardiol 2001; 38:1859–65) © 2001 by the American College of Cardiology

Arterial smooth muscle relaxation is partially mediated by endothelial-dependent mechanisms (1), which involve the release of nitric oxide (2). In vitro, the primary hemodynamic determinant of endothelial release of nitric oxide and subsequent vasodilation is wall shear stress (WSS) (3,4). Wall shear stress has been shown to determine vasodilation in rat cremasteric muscle arterioles (3) and to be regulated by the endothelial release of nitric oxide and vasodilation in the coronary microcirculation of dogs (5). In humans, an increase in blood flow after a brief period of skeletal muscle ischemia is accompanied by dilation of the conduit artery (6,7). Furthermore, an increase in the magnitude or duration of hyperemia leads to increased vasodilation (8,9). However, the relationship between WSS and arterial flow-mediated dilation (FMD) has not as yet been established in humans.

Flow-mediated dilation has been measured in limbs using high-frequency ultrasound. However, the calculation of WSS requires the simultaneous acquisition of dimension and flow information. Ultrasound methods for performing these measurements accurately require special off-line signal processing (10). Moreover, the ultrasound method is critically operator dependent, which can reduce reproducibility.

Ultrasound measurements of FMD have been widely used to study endothelial function in patients with known cardiac risk factors (11,12). However, there is considerable overlap in the arterial dilatory response between individuals with and without cardiac risk factors (8,11,12). This is, in part, because FMD is inversely related to baseline diameter (7). There is evidence from the study of rat skeletal muscle arterioles that this inverse relationship may be due to an inverse relationship between baseline diameter and WSS during hyperemia (3). However, this has not been investigated in humans.

Phase-contrast magnetic resonance angiography (PCMRA) may enhance the investigation of the mechanisms of endothelial-dependent arterial vasodilation. Phase-contrast magnetic resonance angiography readily provides spatially averaged blood flow velocity as well as cross-sectional area. This technique has been well validated in vivo (13–15). Furthermore, a fixed cross-sectional plane can be imaged repeatedly, reducing operator dependence. Phase-contrast

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Abbreviations and Acronyms

A	=	arterial cross-sectional area at peak systole
D	=	arterial lumen diameter at peak systole
FMD	=	flow-mediated dilation
MRI	=	magnetic resonance imaging
n	=	bluntness factor describing a paraboloid flow velocity profile; increasing n means a blunter profile
PCMRA	=	phase-contrast magnetic resonance angiography
V_C	=	blood flow velocity in the center of the arterial cross-section during peak systolic flow
V_{SA}	=	blood flow velocity, spatially averaged across the arterial cross-section at peak systole
WSR	=	wall shear rate at peak systole
WSS	=	wall shear stress at peak systole
μ	=	blood viscosity

magnetic resonance angiography has been used to measure WSS in various arteries (16,17). To our knowledge, PCMRA has not previously been used to relate the shear stress stimulus to the dilation response in endothelial function.

Using PCMRA, we performed this study for three purposes: 1) to assess the relationship between the hyperemic WSS stimulus and the arterial dilation response in normal humans; 2) to examine whether this endothelial stimulus-response relationship could account, at least in part, for why FMD is greater in small arteries; 3) to compare the measurement of brachial artery diameter by PCMRA with the standard ultrasound technique in normal human subjects.

METHODS

Study population. We studied 18 healthy nonsmokers, age range 25 to 46 years, without cardiac risk factors (self-reported) of hypertension, diabetes, hyperlipidemia, obesity or cardiac disease in a first-degree relative. No volunteer was on cardiovascular or acutely vasoactive medications or was acutely ill. For the protocol comparing diameter measurements by ultrasound and PCMRA, we studied nine healthy volunteers, age range 30 to 56 years, with no known coronary disease; however, cardiac risk factors were not excluded. The subjects gave informed consent; all procedures were performed in accordance with institutional guidelines, and the study was approved by our Institutional Review Board.

Study protocol. Peak systolic WSS and vessel dilation in response to hyperemia were measured in the right brachial artery of each subject. Each subject abstained from alcohol, caffeine, milk and food for at least 6 h before the study. A sphygmomanometer cuff was placed on the upper arm. A 3-in. receiver coil was placed on the medial aspect of the arm, outside of the cuff. Electrocardiographic leads were placed on the thorax. The subject was placed supine, head-first, into a 1.5 T magnetic resonance imaging (MRI) scanner (CV/i, General Electric Medical Systems, Milwaukee, Wisconsin) equipped with cardiac gradient coils (40 mT/m, 120 T/m/s). The arm was positioned using coronal, sagittal or axial scout images to ensure that the brachial artery was parallel to the magnet bore. Baseline phase-contrast MR images were obtained (as discussed in the following text). After baseline blood pressure was recorded, the cuff was inflated to at least 10 mm Hg above peak systolic pressure for 5 min. Phase-contrast scans were acquired during cuff occlusion to verify absence of flow during peak hyperemia immediately after cuff deflation and at 1 min after cuff deflation.

MRI protocol. A single imaging plane perpendicular to the brachial artery was prescribed. Each two-dimensional phase-contrast scan yielded 20 magnitude (anatomic) images and 20 corresponding phase (flow velocity) images, reconstructed from 20 interpolated points in the cardiac cycle. Scan duration was 15 s to 25 s. An electrocardiogram (ECG)-gated cine phase-contrast sequence was used. The imaging parameters were: TR 10.8 ms, TE 4.8 ms, field-of-view 8 cm × 8 cm, matrix size 256 × 224 pixels (pixel size: 0.48 mm × 0.31 mm), slice thickness 8 mm, maximum encoded velocity 250 cm/s along the superior/inferior axis, 16 views per segment, first order flow compensation with view-sharing, bandwidth 31.2 kHz, flip angle 25°. The maximum encoded velocity value was chosen to accommodate the greatly increased velocity during peak hyperemia. The field-of-view and matrix size correspond to a pixel resolution of 8.96 pixels/mm^2. An arterial lumen with a circular cross-section diameter of 4 mm would, thus, be represented by 113 pixels. The imaging parameters were in accord with optimal criteria suggested for using MRI to measure blood vessel diameter (18).

Data analysis. Using commercially available flow analysis software (General Electric), the artery lumen at the vessel wall in each image was outlined manually with a region-of-interest tool. At least eight curved segments were placed manually around the lumen-vessel border in the magnitude (anatomic) images. Thus, this method did not constrain the geometry of the lumen perimeter. The cross-sectional area was obtained as the average of three measurements made at the cardiac phase where peak flow occurred. Spatially averaged blood flow velocity (V_{SA}) was calculated from the same specific phase. In calculating average vessel diameter (D) from cross-sectional area (A), a circular cross-section was assumed:

$$D = 2(A/\pi)^{1/2}$$

Peak systolic wall shear rate (WSR) was calculated as:

$$\text{Peak WSR} = 2(n + 2)\,(V_{SA})/D$$

where n determines the bluntness of a paraboloid velocity distribution (10). For a fully developed parabola, n equals 2. The velocity profile in the brachial artery during systole is blunted (19). Thus, n would be expected to be greater than

2. To determine *n*, we calculated the ratio of the center systolic velocity (V_C) to V_{SA} for the two baseline scans and for peak hyperemia in 15 subjects. (Three subjects could not be included in the calculation of mean bluntness factor due to failure of the memory storage medium containing those three studies). For a paraboloid profile,

$$V_{SA} = n\,(V_C)/(n + 2)$$
$$n = 2/([V_C/V_{SA}] - 1)$$

The average V_C/V_{SA} of the 15 subjects was used to calculate *n* for the brachial artery of normal subjects. Peak systolic wall shear stress (peak WSS) was calculated by multiplying peak WSR by blood viscosity. As blood is a non-Newtonian fluid, its viscosity varies at different shear rates (20). After all the shear rates were calculated, a viscosity value was used that corresponded with the observed range of shear rates (21).

Ultrasound correlation protocol. Nine healthy subjects with no known coronary disease, age range 30 to 56 years, underwent the PCMRA protocol and a similar FMD protocol using a standard ultrasound approach. The ultrasound FMD protocol was performed three times for each subject: two times, spaced 15 min apart in the first session and a third time one week later. The ultrasound and PCMRA protocols were carried out at the same time of the day and within three months of each other for each subject. Subjects abstained from food, coffee, alcohol and cigarettes for at least 6 h before the ultrasound test, as with the PCMRA protocol. Electrocardiogram leads were placed on the chest. The skin was marked at a satisfactory probe position approximately 5 cm proximal to the antecubital fossa. An inflatable cuff was placed on the right forearm. A 7.0 MHz ultrasound transducer (Hewlett Packard, Palo Alto, California) was used to image the right brachial artery. After baseline measurements, the cuff was inflated to 200 mm Hg for 5 min, then deflated. The brachial artery was scanned continuously, and images were recorded at 1 min after cuff deflation. The images were recorded on disk. Analyses were performed off-line. As with PCMRA, FMD was calculated as the percent change in diameter from baseline to 1 min after cuff release. The three ultrasound measurements were averaged for each subject.

Statistical analysis. Results are expressed as mean value ± SD. Linear regression analysis was used to: 1) assess the relationship between percent change in diameter and hyperemic peak systolic WSS or change in peak systolic WSS, 2) assess the relationship between baseline diameter and percent change in diameter or hyperemic peak systolic WSS, and 3) compare diameter between ultrasound and PCMRA. A p value less than 0.05 was considered significant.

A Bland-Altman plot was used to compare measurements of diameter between PCMRA and ultrasound (22).

Intraobserver variability of measuring diameter and V_{SA} with PCMRA was calculated at baseline by the coefficient of variation ([100] [SD/mean]) for the 18 normal subjects.

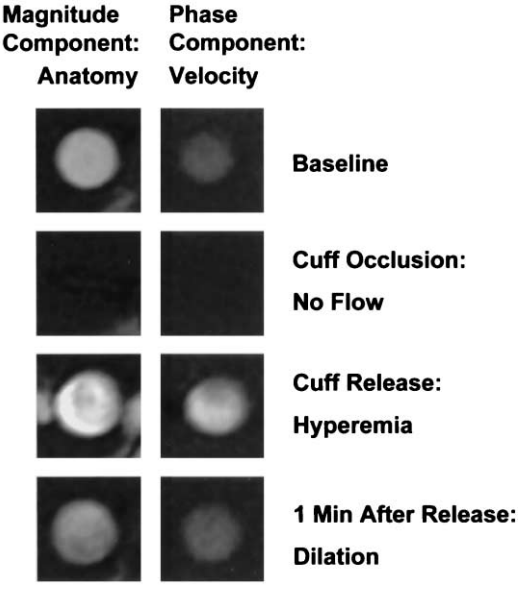

Figure 1. Phase-contrast images of the brachial artery cross-section in a normal subject. Each image consists of a magnitude (anatomic) and a phase (velocity) component. Images were acquired at baseline, during arterial occlusion by cuff inflation (the magnitude component shows the flattened cross-section; the phase component shows absence of flow), during peak hyperemia immediately after cuff release and at 1 min after cuff release, when flow-mediated dilation had occurred. The images are smoothed (but the raw data used for measurements and calculations are unaffected).

To calculate interobserver variability of the PCMRA technique, images from eight of the subjects were analyzed by two observers who were blinded to the subjects' identities and to each other's measurements. Each observer independently circumscribed cross-sectional area three times. Interobserver coefficient of variation was calculated for arterial diameter and V_{SA}.

RESULTS

Relationship between shear stimulus and dilation response by PCMRA. The average resting blood pressure in the normal subjects was: systolic, 116 ± 15 mm Hg; diastolic, 69 ± 7 mm Hg. Magnitude (anatomic) and phase (velocity) images during peak systolic flow are shown for a typical subject at baseline, during cuff occlusion, during maximum hyperemia immediately after cuff release and at 1 min after cuff release (Fig. 1). Increased blood flow velocity is linearly encoded as higher intensity in the phase images. Areas of increased blood flow also have a higher intensity in the magnitude images due to nonlinear flow effects.

Average V_C/V_{SA} for the subset of 15 subjects was 1.69 ± 0.16 and did not change during peak hyperemia (1.69 ± 0.21, p = 0.87). Thus, bluntness factor $n = 3.0 \pm 0.8$ at baseline (range: 2.1 to 4.6) and did not change significantly during hyperemia (n = 3.2 ± 1.0, range: 2.1 to 4.6, p = 0.25). Therefore $n = 3$ was used to calculate systolic WSR.

Velocity profiles at baseline and during peak hyperemia are shown for the individuals with the lowest *n*, highest *n*

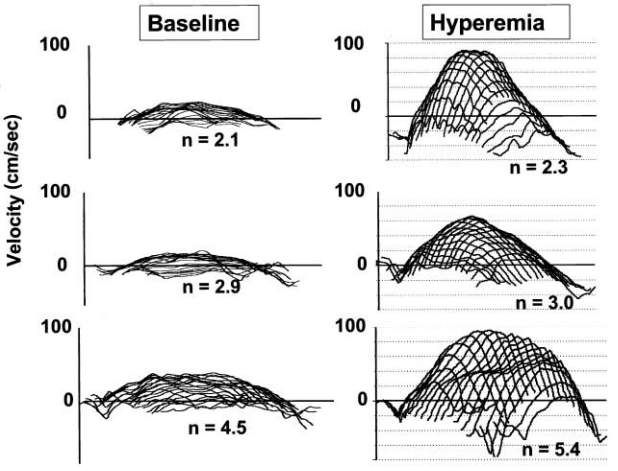

Figure 2. Blood flow velocity profile at baseline and at peak hyperemia for three subjects with different bluntness factor **n**: the subject with smallest **n** (least blunt profile, **top row**), a subject with **n** close to the average **(middle row)** and the subject with greatest **n** (bluntest profile, **bottom row**).

and *n* value closest to the average of the 15 subjects used to calculate the mean *n* (Fig. 2). For the range of shear rates encountered in this study (342 to 2,145 s^{-1}), blood viscosity (μ) varies between 0.0032 and 0.0034 N-s/m^2 (21). Therefore, we used μ = 0.0033 N-s/m^2 to calculate peak WSS. Peak WSS increased from 1.68 ± 0.34 N/m^2 at baseline to 5.03 ± 1.37 N/m^2 immediately after cuff release ($p < 0.0001$) (Table 1). Vessel diameter increased from 3.84 ± 0.60 mm at baseline to 4.34 ± 0.58 mm 1 min after cuff release ($p < 0.0001$) (Table 1). The relationship between peak systolic WSS during peak hyperemia and percent change in diameter from baseline to 1 min after cuff release is shown in Figure 3A. Percent change in diameter is linearly proportional to peak systolic WSS during hyperemia with a high correlation ($r = 0.79$, $p = 0.0001$). Percent change in diameter is also linearly proportional to the change in peak systolic WSS from baseline to hyperemia ($r = 0.70$, $p = 0.001$) (Fig. 3B).

Variability. The intraobserver coefficient of variation was 1.0% for diameter (range: 0.3% to 2.1%) and 3.1% for V_{SA} (range: 0.5% to 6.3%). Interobserver coefficient of variation was 2.3% for diameter (range: 0.4% to 5.7%) and 4.2% for V_{SA} (range: 0.5% to 12.0%).

PCMRA compared with ultrasound. In the study group comparing PCMRA with ultrasound, two subjects had one or more cardiac risk factors. A Bland-Altman plot comparing the brachial artery diameter measurements between ultrasound and PCMRA is shown in Figure 4. The measurements were highly correlated at baseline and at 1 min (overall $r = 0.84$, $p < 0.01$), but diameter was greater by PCMRA than by ultrasound (4.1 ± 0.7 mm vs. 3.7 ± 0.5 mm, $p = 0.009$) (Table 2).

Relationship between FMD and baseline diameter. Flow-mediated dilation was inversely related to baseline diameter ($r = 0.62$, $p = 0.006$). However, systolic WSS during peak hyperemia was also inversely related to baseline diameter ($r = 0.47$, $p = 0.049$). Thus, the greater FMD response in small arteries appears to be accounted for, at least in part, by the greater hyperemic WSS stimulus in small arteries.

DISCUSSION

In this study, we describe a method to assess vascular endothelial function using PCMRA. This is, to our knowledge, the first report quantifying the relationship between wall shear stress during peak postischemic hyperemia and resulting arterial dilation in humans. By obtaining spatially averaged flow velocity and cross-sectional area simultaneously, we were able to calculate peak vascular WSS and arterial lumen diameter at baseline, during hyperemia and at 1 min after peak hyperemia. We showed that peak systolic WSS during peak hyperemia is linearly proportional to the resulting diameter percent change from baseline. Our results also suggest that the FMD response is greater in small arteries, at least in part, because the hyperemic WSS stimulus is greater in small arteries.

Stimulus and response in FMD. Shear stress is considered to be the primary mechanical stimulus in FMD (23,24). In humans, the effect of varying the hyperemic response was studied by varying the duration of forearm cuff occlusion, demonstrating that greater increases in flow produce greater dilation (9). In hypertensive individuals, reduced FMD is due, at least in part, to lower baseline systolic WSS (25). Using PCMRA, our study is the first to provide a quantitative relationship between peak WSS during peak hyperemia and FMD in normal individuals. Thus, measuring peak WSS during postocclusion hyper-

Table 1. Subject Characteristics and Measurements

			Diameter (mm)			V_{SA} (cm/s)		Sys. WSS (N/m^2)	
Gender	#	Age	Base	1 Min	%Δ	Base	Peak	Base	Peak
Men	7	34	4.40	4.88†	11.0	19.8	62.4†	1.68	5.03†
		(4)	(0.49)	(0.52)	(4.2)	(5.1)	(14.3)	(0.34)	(1.37)
Women	11	33	3.49	3.99*	14.7	18.1	60.2*	1.72	5.31*
		(7)	(0.34)	(0.27)	(5.0)	(3.4)	(15.0)	(0.30)	(1.53)
All	18	33	3.84	4.34*	13.3	22.3	65.8*	1.68	5.03*
		(6)	(0.60)	(0.58)	(5.0)	(6.5)	(13.5)	(0.34)	(1.37)

*Indicates change from baseline ($p < 0.0001$); †($p < 0.001$).

= number of subjects; Base = baseline value; Diameter 1 min = diameter at 1 min after cuff release; Peak = peak hyperemia immediately after cuff release; Sys. WSS = systolic wall shear stress; V_{SA} = blood flow velocity, spatially averaged across the arterial cross-section at peak systole.

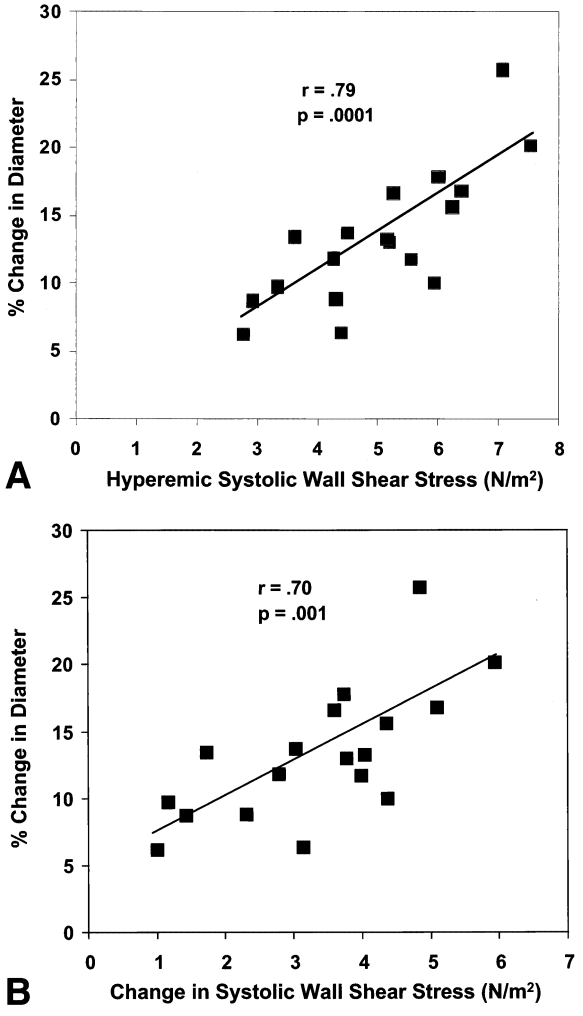

Figure 3. **(A)** Flow-mediated dilation (FMD) (percent change in diameter at 1 min after cuff release) is linearly proportional to systolic wall shear stress during peak hyperemia (WSS_{hyp}, systolic wall shear stress immediately after cuff release). FMD = 2.9 (WSS_{hyp}) − 1.1. **(B)** FMD is also linearly proportional to the change in systolic wall shear stress (ΔWSS, change from baseline to peak hyperemia immediately after cuff release). FMD = 2.5 (ΔWSS) + 5.0.

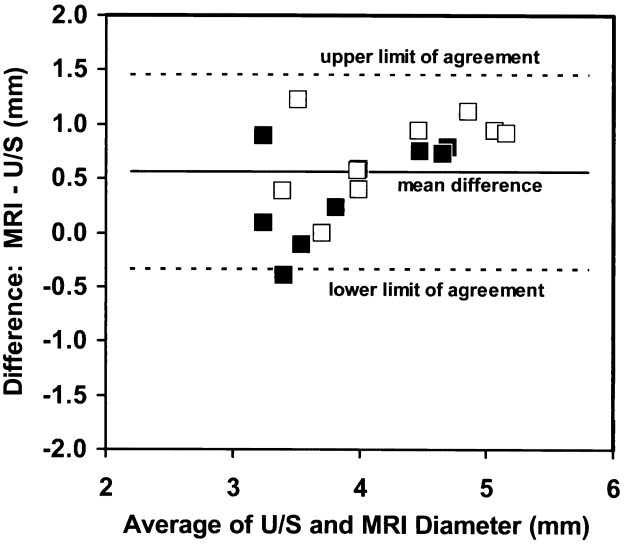

Figure 4. Bland-Altman plot: difference between diameter by phase-contrast magnetic resonance angiography (PCMRA) and ultrasound (U/S) plotted against average diameter by PCMRA and U/S. Also shown are 95% limits of agreement (mean ± 2 SD). Diameter is greater by PCMRA. **Solid square** = baseline; **open square** = 1 min. after release of occlusion. MRI = magnetic resonance imaging.

emia may relate stimulus to response in endothelial-dependent FMD.

Our study suggests that vessel size may be an important determinant of the hyperemic wall shear stress stimulus in FMD. Future studies will be needed to determine any gender differences in the hyperemic wall shear stress stimulus for a given artery diameter. Of note, even in the 11 women in this study population, the inverse relationship between hyperemic WSS and baseline diameter approaches significance ($r = 0.54$, $p = 0.08$).

The intraobserver variation in measuring diameter by PCMRA was 1.0%, which is similar to the 1.9% described in the ultrasound literature (8). The interobserver variation was 2.3%, which is similar to the 1% to 3% described in the ultrasound literature (11).

Measurement of WSS. The WSS value calculated using our method is an indirect estimate of the mean WSS value, and the value should be evaluated against other reported methods. Simon et al. (19) measured peak systolic WSR and peak systolic WSS at rest in the brachial artery. Using a special micrometric ultrasound technique, they measured the velocity profile and employed Womersley's method of calculating WSR and WSS for a straight, distensible artery with pulsatile flow. In normal subjects, the average peak systolic WSR was 484 s^{-1}. In our study the average peak WSR was 510 s^{-1}, a difference from their value of only 5.4%. In four subjects, the authors compared the use of Womersley's method with the method of direct measurement, in which WSR is obtained by measuring the slope of the velocity profile at the artery wall. For those subjects, the average peak systolic WSR differed between the two methods by less than 1%.

Our method of obtaining WSS differs somewhat from a previously reported PCMRA-based method by Oyre et al. (16,17). Their elegant method examines only the velocity pixels near the vessel wall, in sectors around the circumference, and curve-fits a fully developed paraboloid to the pixels in each sector. The WSS is then the slope of the paraboloid at the vessel boundary. In contrast, our method utilizes all of the pixels in the cross-section to calculate the mean WSS on the entire vessel circumference. Including all of the pixels may be very important in smaller arteries (such as the brachial artery) as opposed to carotid arteries where their approach was utilized. Our method is also simpler to implement. However, the method by Oyre at al. (16,17) is a more direct assessment of WSS and may be theoretically advantageous in complex anatomic situations such as bifurcations of large arteries. Both methods account for a skewed, blunted velocity profile.

Table 2. Comparison of Diameter Measurements Between Ultrasound and MRI

		D base (mm)		D 1 min (mm)		ΔD (mm)		% ΔD (mm)	
Subject	**Age**	**U/S**	**MRI**	**U/S**	**MRI**	**U/S**	**MRI**	**U/S**	**MRI**
Mean	40	3.70	4.09†	3.88	4.60‡	0.18	0.50*	4.4	12.4*
(St Dev)	(8)	(0.50)	(0.75)	(0.60)	(0.79)	(0.14)	(0.14)	(2.9)	(3.8)
Range	30–46	2.8–4.3	3.21–5.09	2.90–4.70	3.58–5.61	0.00–0.40	0.29–0.70	0.0–7.0	8.8–20.1

*Indicates a difference between the two modalities ($p < 0.0001$); †($p = 0.001$); ‡($p = 0.03$).
D base = baseline diameter; D 1 min = diameter at 1 min after cuff release; MRI = diameter measurement by magnetic resonance imaging; U/S = measurement by ultrasound.

Potential of assessing endothelial function by PCMRA. In assessing FMD by PCMRA, a fixed cross-sectional plane can be imaged repeatedly. This eliminates the need for an operator to ensure that a probe is capturing the true diameter of the same arterial cross-section during each acquisition. By reducing operator dependence, PCMRA may improve reproducibility.

Because PCMRA provides cross-sectional area and flow velocity simultaneously, it readily allows for the calculation of wall shear stress, the stimulus for FMD. Since the magnitude of postischemic hyperemia and, thus, hyperemic peak WSS varies among individuals, the stimulus for FMD cannot easily be controlled. Therefore, comparing the magnitude of the stimulus to the magnitude of the response may enhance the ability to identify endothelial dysfunction in individuals.

Assumptions. We assumed that the velocity profile during peak systole is a blunted paraboloid. This assumption is supported by studies on pulsatile flow in distensible tubes (20,26) and by actual measurements in the brachial artery using special micrometric ultrasound (19). Our data actually show the velocity profile to be slightly skewed; that is, the peak of the paraboloid is not at the exact center of the arterial cross-section. However, the average fractional distance (distance divided by radius) from the location of the maximum flow velocity to the center of the arterial cross-section was only 0.27. With this fractional distance, the difference between assuming symmetry and skewness in calculating peak systolic WSS averaged around the arterial circumference is only 2%.

Differences between PCMRA and ultrasound protocols. There were differences in the way diameter was obtained using PCMRA and ultrasound. With ultrasound, the diameter measurements cannot readily be timed to peak flow and are commonly made at the time of the R wave, as in this study. With PCMRA, they were made at peak flow because that is the time of peak signal contrast between the lumen and the vessel wall. This explains, at least in part, why the vessel diameter is larger by PCMRA.

In the PCMRA protocol, the occluding cuff was placed on the upper arm to maximize sensitivity in measuring FMD. This is because hyperemia and FMD are greater after upper arm occlusion than after lower arm occlusion (27). The cuff was placed on the lower arm in the ultrasound protocol to maximize stability in imaging the brachial artery. Thus FMD was greater using the PCMRA protocol ($p < 0.0001$).

Another factor that may introduce variability in comparing PCMRA and ultrasound measurements is that the two studies were spaced as much as three months apart for a given subject.

Study limitations. Instantaneous flow-velocity is not measured in calculating hyperemic WSS. However, because the stimulus to dilate requires some finite duration of supranormal flow (8,9), then hyperemic WSS during the 15-to-25 s interval of its peak occurrence may be a more important measurement of stimulus than instantaneous WSS.

One theoretical limit in determining lumen dimension accuracy is spatial resolution. The parameters in this study yield a linear spatial resolution of 0.31 mm. However, by measuring cross-sectional area, the effective linear resolution is improved over measuring one diameter in one dimension. For example, a 4-mm diameter cross-section is represented by approximately 113 pixels. Nevertheless, at the present time, spatial resolution is probably better with current ultrasound techniques, with resolution reported as small as 0.065 mm (28). An accuracy and reproducibility study using PCMRA needs to be performed and compared with the standard ultrasound reproducibility study (28).

Our temporal resolution does not ensure that the precise peak of the arterial cross-sectional area and flow within a cardiac cycle is acquired. However, the scans are gated to the R wave of the ECG. Therefore, the images are acquired at a similar relative time for each subject, enabling reasonable comparisons within subjects and between subjects. Furthermore, the error in missing the exact peak hyperemic velocity within the cardiac cycle is small compared with the great increase in overall velocity from baseline.

Conclusions. Using PCMRA in the brachial artery of healthy individuals, we showed that the FMD response is linearly proportional to the systolic WSS stimulus that occurs during peak hyperemia. Furthermore, our findings that suggest that the greater FMD response in small arteries is, at least in part, because the hyperemic WSS stimulus is greater in small arteries.

Phase-contrast magnetic resonance angiography provides cross-sectional area and spatially averaged blood flow velocity simultaneously; thus, it readily allows for the calculation of vascular WSS as well as degree of dilation. A fixed cross-section can be imaged repeatedly, reducing operator

dependence. By quantifying the stimulus-response relationship in FMD, PCMRA may improve the distinction between normal and abnormal endothelial function.

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