Local Shear Stress and Brachial Artery Flow–Mediated Dilation

The Framingham Heart Study

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Abstract—Endothelium-dependent flow-mediated dilation is a homeostatic response to short-term increases in local shear stress. Flow-mediated dilation of the brachial artery in response to postischemic reactive hyperemia is impaired in patients with cardiovascular disease risk factors and may reflect local endothelial dysfunction in the brachial artery. However, previous studies have largely neglected the effect of risk factors on evoked shear stress, which is the stimulus for dilation. We evaluated brachial artery percent dilation and evoked diastolic shear stress during reactive hyperemia using high-resolution ultrasound and Doppler in 2045 participants (1107 women, mean age 61 years) in the Framingham Offspring Study. In age- and sex-adjusted models, baseline and hyperemic shear stress were related to brachial artery percent dilation. In stepwise multivariable analyses examining clinical correlates of percent dilation (without shear stress in the model), age, sex, mean arterial pressure, pulse pressure, heart rate, body mass index, lipid medication use, and hormone replacement therapy were related to percent dilation (R^2=0.189; P<0.001). When hyperemic shear stress was incorporated, the overall R^2 improved (R^2=0.335; P<0.001), but relationships between risk factors and percent dilation were attenuated (age and mean arterial pressure) or no longer significant (all others). In contrast, risk factors were related to baseline and hyperemic shear stress in multivariable analyses. Evoked hyperemic shear stress is a major correlate of brachial artery flow–mediated dilation. The associations between many risk factors and brachial artery flow–mediated dilation may be attributable to reduced stimulus for dilation rather than impaired local conduit artery response during hyperemia. **(*Hypertension*. 2004;44:134-139.)**

Key Words: endothelium ■ microcirculation ■ risk factors

Local shear stress (SS) has important short- and long-term effects on the vascular endothelium that are relevant to atherogenesis.[1,2] Under normal conditions, the vascular endothelium responds to short-term increases in flow by releasing NO and other endothelium-dependent relaxing factors that dilate the artery and reduce SS toward normal.[3] Flow-mediated dilation (FMD) is impaired in atherosclerotic coronary arteries,[4] although the response is maintained in patients with hypercholesterolemia and angiographically normal arteries.[5] FMD has been studied noninvasively in the brachial artery by using reactive hyperemia after a short period of forearm ischemia as the flow stimulus and evaluating percentage increase in brachial artery diameter (FMD%).[6] Brachial artery FMD% is impaired in patients with cardiovascular disease risk factors (CRFs) or coronary atherosclerosis.[7]

Reactive hyperemia largely reflects dilation of resistance vessels by ischemia-induced production of vasodilators including NO.[8] Although not widely appreciated, some studies have demonstrated a reduction in reactive hyperemia in patients with CRFs[9,10] or coronary artery disease.[7] Because reactive hyperemia is the stimulus, we hypothesized that reduced FMD in the presence of CRFs could reflect diminished stimulus rather than a local abnormality of the brachial artery endothelium. The relative degree of impairment of conduit and resistance vessel vasodilator function determines the net response of the conduit artery and may have physiological and prognostic implications.[11] To better define the interrelations of systemic CRFs, FMD, and local SS, we performed ultrasound measurements of the flow and diameter responses to forearm cuff occlusion in a large, well-characterized community-based cohort.

Methods

Study Participants

Details of the patient examination have been published.[12] Participants in the seventh examination cycle (1998 to 2001) were eligible

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for the present investigation (n=3539). Studies were performed on 2640 participants after implementation of the tonometry and digital Doppler acquisition program; 2325 had analyzable Doppler data, 2271 had full tonometry, and 2454 had analyzable brachial artery diameters, resulting in a final sample of 2045 individuals with all elements of the testing. The Boston Medical Center institutional review board approved the protocol, and each participant gave written informed consent. The procedures followed were in accordance with institutional guidelines.

Ultrasound Data Acquisition

The brachial artery images and Doppler flow were assessed with a Toshiba SSH-140A ultrasound system and 7.5-MHz linear array transducer before and after arterial flow was interrupted for 5 minutes by a cuff placed on the proximal forearm.[12] Using a carrier frequency of 3.75 MHz and an insonation angle of ≈60°, Doppler flow was assessed at baseline and for the initial 15 seconds after cuff deflation to document baseline and peak hyperemic flow.[6] All flow values were corrected for actual insonation angle.

Image and Flow Analyses

Brachial artery baseline (D_{BL}) and 60-second postdeflation diameter (D_{DF}) were measured as described previously.[12] FMD was expressed as relative change from baseline: $FMD\% = (D_{DF} - D_{BL})/D_{BL}$.

Flows were analyzed from the digitized audio data using a semiautomated signal-averaging approach.[13] Sonographers analyzed diameters, and on a separate occasion, measured flows with no knowledge of clinical status or the corresponding FMD%. Raw flow spectra were displayed and cardiac cycles with artifacts were excluded by the sonographer. During hyperemia, peak flow timing was confirmed visually, and only beats representing the peak flow response were included in the signal-averaged spectrum. Flow spectra were then signal averaged (1000-Hz resolution) using the ECG as a fiducial point. The pulsatile flow velocity waveform for the signal-averaged cardiac cycle was established automatically by finding the median flow velocity at each point in the flow spectrum. Onset of diastole was defined from the timing of the dicrotic notch on a brachial pressure waveform obtained by tonometry just before FMD evaluation. The hyperemic mean flow ratio was calculated by dividing mean flow during hyperemia by mean flow at baseline. Flow velocity (V) was converted to local SS using the following equation: $SS_x = 8 \times \mu \times V_x/D_{BL}$, where the subscript x indicated either baseline or hyperemia, and μ was viscosity of blood, which was assumed to be 0.035 dyne×s/cm^2. To assess reproducibility of flow measurement, flows were reanalyzed blindly in a random sample of 50 individuals. This approach assesses measurement but not biological variability in flow. Systolic, diastolic, and mean flows were highly reproducible at baseline and during deflation with a correlation of >0.98 for all paired comparisons. Measurement variability of brachial artery diameter and FMD has been reported previously[12] and was comparable to reports from other laboratories.

Statistical Analysis

Baseline characteristics, FMD%, and flow variables were tabulated separately by sex. Values are presented as mean±SD except as noted. Regression was performed using the SAS REG procedure.[14,15] Stepwise multivariable regression (with age and sex forced into the model) was used to select correlates of baseline brachial artery diameter and FMD% from the following covariates with $P \leq 0.10$ for inclusion: mean arterial pressure (MAP), pulse pressure, heart rate, diabetes, current cigarette smoking, smoking within 6 hours before the examination, total/high-density lipoprotein cholesterol, triglycerides, body mass index (BMI), glucose, hypertension treatment, lipid treatment, daily aspirin use, hormone replacement therapy, prevalent cardiovascular disease, and walk test. Two variables coded whether walk test was done before or after brachial reactivity versus not done. These variables entered models together or not at all. Models were repeated with shear or flow as an additional candidate. Regression coefficients were expressed per SD of the independent variables or for presence of a specified value (eg, female gender). Partial R^2 values represent the change in R^2 as each variable entered the model. A 2-sided $P<0.05$ was considered significant.

TABLE 1. Study Sample Characteristics

Variable	Men (n=938)	Women (n=1107)
Age, years	61±10	61±9
MAP, mm Hg	95±11	89±12
Pulse pressure, mm Hg	51±14	54±15
Heart rate, bpm	62±11	65±10
BMI, kg/m^2	28.2±4.0	26.7±4.9
Total/HDL cholesterol ratio	4.5±1.4	3.6±1.2
Triglycerides, mg/dL	143±108	128±75
Fasting glucose, mg/dL	108±29	99±23
Prevalent cardiovascular disease, %	17	9
Diabetes, %	16	9
Hypertension, %	49	41
Antihypertensive medication, %	36	29
Lipid-lowering medication, %	24	17
Daily aspirin use, %	37	22
Smoking previous year/6 hours, %	13/8	14/9
Walk test before/after/not done, %	38/35/27	40/39/21
Hormone replacement therapy, %	0	37
Baseline		
Mean flow velocity, cm/s	8.7±5.2	7.5±4.6
Systolic flow velocity, cm/s	22.7±8.0	22.3±8.5
Diastolic flow velocity, cm/s	2.0±4.5	−0.5±3.7
DSS, dyne/cm^2	1.1±2.6	−0.4±3.0
Hyperemia		
Mean flow velocity, cm/s	47.8±20.3	54.0±21.7
Systolic flow velocity, cm/s	68.6±23.1	77.7±25.1
Diastolic flow velocity, cm/s	37.8±19.5	41.0±20.8
DSS, dyne/cm^2	22.1±12.2	32.6±18.1
Hyperemic mean flow ratio	7.2±4.9	9.1±5.5

Results

Sample characteristics are presented in Table 1. In this middle-aged to elderly cohort (33 to 88 years), baseline brachial artery diastolic flow velocity was quite low (Table 1); in 53% of the participants, average diastolic flow was zero or reversed (Figure 1). The hyperemic mean flow response to ischemia was substantial (9-fold in women, 7-fold in men; Table 1) but highly variable. Baseline brachial artery diameter was 3.7±0.6 mm in women and 4.9±0.6 mm in men. During hyperemia, the brachial artery dilated 3.3±3.0% in women and 2.3±2.4% in men. Age- and sex-adjusted relations of flow variables with brachial measures are presented in Table 2. Higher baseline diastolic flow and diastolic SS (DSS) were associated with larger baseline diameter and higher FMD%. Hyperemic flow, whether measured during systole or diastole, or averaged across the cardiac cycle, and DSS were strongly and directly related to FMD% (Table 2, Figure 2), whereas the hyperemic mean flow ratio was less closely related to FMD% (Table 2).

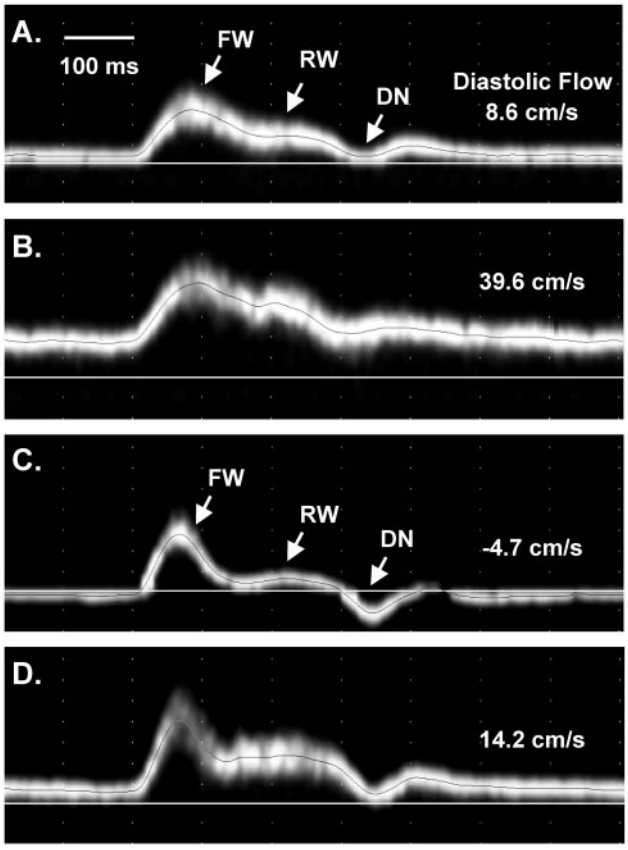

Figure 1. Examples of signal-averaged flow spectra at baseline and after 5 minutes of forearm ischemia. The first example is an individual with persistently positive brachial artery flow at baseline (A) and a vigorous flow response during reactive hyperemia (B). The second example is from a participant with flow reversal in the brachial artery during diastole at baseline (C) and a blunted flow response during hyperemia (D). Flow augmentation, attributable to wave reflections returning from elsewhere in the body (RW), is clearly evident in mid-to-late systole after the peak of the forward wave (FW) at baseline (A and C) and is enhanced during hyperemia (B and D). Note that the initial systolic flow pulse amplitude, which is related to local pulse pressure and pulse wave velocity, changes relatively little during hyperemia, whereas flow associated with the remote RW and flow during diastole changes considerably (B). For this reason, we have focused on diastolic flow and DSS stress in the multivariable analyses. DN indicates dicrotic notch, corresponding to the onset of diastole. Vertical scale tics are 20 cm/s apart. Average diastolic flow is indicated to the right of each panel.

In stepwise regression models, when no consideration was given to baseline or hyperemic SS or flow, several CRFs were related to FMD% (Table 3). Thus, increasing age, need for lipid-lowering medication, and higher MAP, pulse pressure, and BMI were associated with lower FMD%, whereas female gender, hormone replacement therapy, and higher heart rate were associated with higher FMD% (model $R^2=0.189$; $P<0.001$; Table 3). When hyperemic DSS was considered as an additional covariate, relationships between CRFs and FMD% were weakened, whereas the overall model R^2 improved (model $R^2=0.335$; $P<0.001$; Table 3). The effects of age and MAP remained significant, indicating that FMD% was reduced with advancing age and higher MAP, even after considering variability in the flow response. However, effect sizes for age and MAP were reduced considerably (to one fourth and one half of their original values, respectively) when shear response was considered in the model. Sex was retained in the model by design but was no longer significant, whereas other CRFs either did not enter the model (BMI, pulse pressure, hormone replacement therapy, and heart rate) or were no longer significant (lipid-lowering therapy). In contrast, when the hyperemic mean flow ratio, which is the measure of flow used in most previous studies,[6] was evaluated as a covariate rather than DSS, the model fit was only minimally changed ($R^2=0.194$) relative to the model with no flow variable ($R^2=0.189$), and all CRFs that appeared in the model without flow incorporated remained significant.

TABLE 2. Age- and Sex-Adjusted Models for Baseline Brachial Artery Diameter and FMD%

	Baseline (mm)		FMD%	
Variable (SD)	Estimate	*P*	Estimate	*P*
Baseline				
Mean flow velocity (4.9 cm/s)	0.00	0.865	0.25	<0.001
Systolic flow velocity (8.2 cm/s)	−0.05	<0.001	0.19	<0.001
Diastolic flow velocity (4.3 cm/s)	0.07	<0.001	0.27	<0.001
DSS (2.9 dyne/cm^2)	0.06	<0.001	0.31	<0.001
Hyperemia				
Mean flow velocity (21.3 cm/s)	−0.11	<0.001	1.23	<0.001
Systolic flow velocity (24.6 cm/s)	−0.13	<0.001	1.04	<0.001
Diastolic flow velocity (20.3 cm/s)	−0.09	<0.001	1.30	<0.001
DSS (16.5 dyne/cm^2)	−0.27	<0.001	1.51	<0.001
Hyperemic mean flow ratio (5.3)	−0.07	<0.001	0.34	<0.001

Because brachial artery diameter was included in the equations for FMD% and DSS, the possibility existed that the relationship between DSS and FMD% was predominantly mathematical rather than physiological. Therefore, we also evaluated models with actual change in brachial artery diameter (in millimeters) rather than FMD% as the dependent variable and hyperemic diastolic flow velocity rather than DSS as a potential covariate. Once again, when flow velocity was allowed to enter this model, the overall R^2 improved (from 0.146 to 0.269), the change in R^2 when flow entered the model was high (partial $R^2=0.165$; $P<0.001$), and age (partial $R^2=0.095$; $P=0.006$), sex (partial $R^2<0.001$; $P=0.028$), and MAP (partial $R^2=0.007$; $P<0.001$) were the only other significant correlates of diameter change.

We next evaluated correlates of baseline and hyperemic DSS and found relationships with several CRFs (Table 4). Increasing age and pulse pressure were associated with reductions in baseline and hyperemic DSS. Walk test before brachial testing was associated with higher baseline DSS. Higher BMI was associated with increased baseline but reduced hyperemic DSS. Higher MAP, prevalent CVD, prescribed antihypertensive treatment, and fasting glucose were associated with blunted hyperemic DSS, whereas female gender, hormone replacement therapy, and higher baseline DSS were associated with increased hyperemic DSS.

To determine whether the associations between hyperemic DSS and CRFs were affected by age or sex, we repeated the hyperemic DSS model separately for individuals above ver-

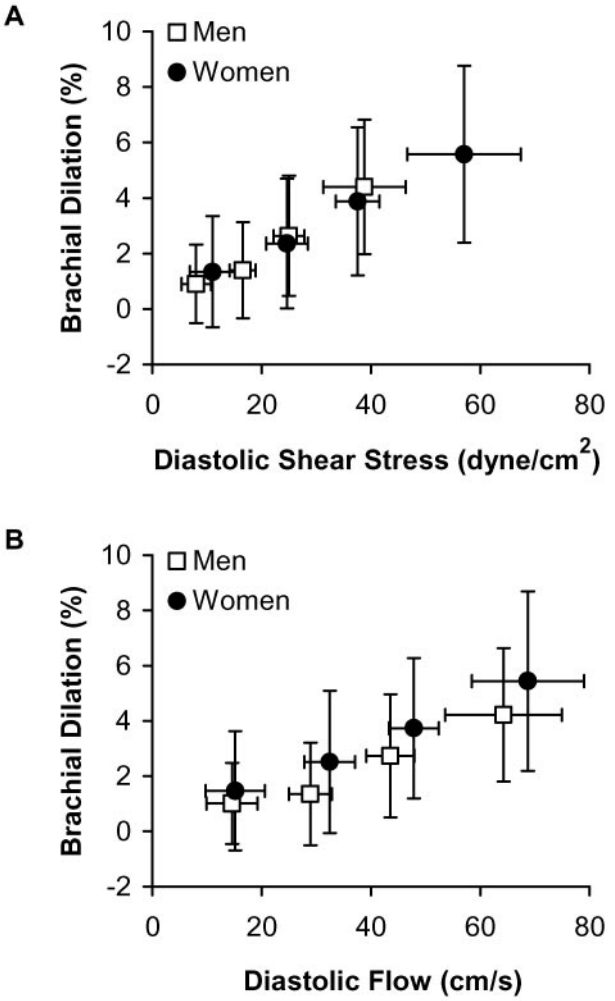

Figure 2. Brachial artery dilation according to sex-specific quartiles of hyperemic DSS (A) and flow (B). Values represent quartile mean±SD. Note that increased FMD% in women vs men appears to be attributable largely to higher hyperemic stimulus, especially when considered in terms of SS (A).

sus below the median age (60 years) and for men versus women. The results were substantially the same in each subgroup, with age, sex, baseline DSS, brachial pulse pressure, BMI, and MAP accounting for most of the variance in hyperemic DSS explained by the models.

Discussion

This study demonstrated that local brachial artery SS, at baseline and especially during reactive hyperemia, was strongly related to brachial artery FMD in the Framingham Heart Study Offspring Cohort. When considering the pulsatile aspects of brachial artery flow, we observed that flow and SS underwent a dramatic transition from diastolic stasis or flow reversal in many individuals at baseline to persistent forward flow during reactive hyperemia. Although systemic CRFs were associated with a reduction in FMD%, those relationships were markedly weakened or absent when hyperemic DSS was included in multivariable models. In contrast, several CRFs and prevalent cardiovascular diseases were related significantly to hyperemic DSS, which reflects

TABLE 3. Brachial Artery FMD% Models

	No Shear Variable*		Include DSS†	
Variable (SD)	Estimate	*P*	Estimate	*P*
Age (9.5 years)	−0.70	<0.001	−0.16	0.008
Sex, (female)	0.43	0.002	−0.08	0.452
Hyperemic DSS (16.5 dyne/cm^2)	—	—	1.42	<0.001
MAP (12.2 mm Hg)	−0.52	<0.001	−0.22	<0.001
Lipid-lowering therapy	−0.39	0.009	−0.23	0.088
Brachial pulse pressure (14.7 mm Hg)	−0.16	0.027	—	—
BMI (4.6 kg/m^2)	−0.17	0.005	—	—
Hormone replacement therapy	0.40	0.012	—	—
Heart rate (10.7 bpm)	0.13	0.028	—	—
Walk test after FMD	−0.03	0.852	−0.07	0.639
Walk test before FMD	0.25	0.111	0.23	0.101

*Model R^2=0.284, P<0.001.
†Model R^2=0.438, P<0.001.

vasodilator function of forearm resistance vessels. Thus, the observed impairment of brachial artery FMD in participants with CRFs may be attributable partially to microvascular dysfunction and a reduction in the stimulus for dilation rather than an intrinsic abnormality of local conduit brachial artery endothelial function.

Several previous studies have reported that CRFs impair brachial artery FMD. For example, impaired FMD relates to older age, male gender, higher blood pressure, insulin resistance, obesity, smoking, and lipid abnormalities and inversely to estrogen therapy.[16] We recently confirmed many of these associations in a large community-based sample.[12] We have now shown that the relationships between FMD and CRFs

TABLE 4. Brachial Artery DSS Models

	Baseline DSS*		Hyperemic DSS†	
Variable (SD)	Estimate	*P*	Estimate	*P*
Age (9.5 years)	−0.76	<0.001	−5.18	<0.001
Sex (female)	−1.24	<0.001	8.54	<0.001
Baseline DSS (2.9 dyne/cm^2)	—	—	2.98	<0.001
Brachial pulse pressure (14.7 mm Hg)	−0.54	<0.001	−1.24	<0.001
BMI (4.6 kg/m^2)	0.46	<0.001	−1.67	<0.001
Smoking	1.07	<0.001	—	—
Aspirin use	−0.29	0.025	—	—
Total/HDL cholesterol ratio (1.3)	0.15	0.012	—	—
Walk test after FMD	0.18	0.238	—	—
Walk test before FMD	0.42	0.007	—	—
MAP (12.2 mm Hg)	0.11	0.084	−3.19	<0.001
Prevalent cardiovascular disease	—	—	−2.47	0.006
Antihypertensive treatment	—	—	−1.95	0.003
Hormone replacement therapy	—	—	2.33	0.003
Fasting glucose (26.4 mg/dL)	—	—	−0.62	0.038

*Model R^2=0.284, P<0.001.
†Model R^2=0.438, P<0.001.

may be secondary in part to the associations between CRFs and abnormal baseline and hyperemic flow and shear. Our results are consistent with a few studies that demonstrated impaired hyperemic flow responses in patients with CRFs[9,10] or established coronary artery disease,[7] including several that carefully measured flow changes using venous occlusion plethysmography.[7,10] None of those studies examined flow and CRFs in the same multivariable model. Furthermore, most of the available studies demonstrated no significant effect of CRFs on hyperemic flow or ignored changes in flow completely. Many of the former studies that evaluated flow focused on the hyperemic mean flow ratio, a variable that correlated much less strongly with FMD% compared with diastolic flow or DSS (Table 2). Thus, our study differs from previous work because of the more careful assessment of flow, the particular attention to diastolic flow and DSS, and most important, because of the much larger sample size, which allowed us to construct multivariable models that simultaneously assessed the effects of CRFs and the stimulus for dilation.

The mechanisms accounting for impaired hyperemic flow in setting of CRFs remain uncertain. Reactive hyperemia is a complex response that reflects tissue production of a number of flow- and ischemia-induced vasodilators as well as direct myogenic responses.[17] A portion of the hyperemic response can be inhibited by infusion of the NO synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA), suggesting that NO plays a role that might be impaired by CRFs.[8,10] In support of this possibility, a recent study demonstrated that hyperemic flow responses were impaired and inhibited to a lesser extent by L-NMMA in patients with hypertension compared with normotensive individuals.[10] Hypertension and aging are associated with important structural changes in microvessels that may contribute to blunted reactive hyperemia. For example, histological studies demonstrate increased medial thickness and other evidence of microvascular hypertrophy in experimental animals[18,19] and in elderly and hypertensive patients.[20] Microvascular abnormalities related to insulin resistance have been described and include vascular rarefaction and abnormal capillary recruitment.[21,22] Obesity-related microvascular dysfunction has also been described.[23] Hypercholestolemia has been associated with reduced reactive hyperemia,[9] and statin drugs have improved flow response.[24] Interestingly, structural changes in the microcirculation correlate strongly with pulse pressure, suggesting that there may be links between CRFs, stiffness of the central aorta, and microvascular dysfunction.[25]

Our study had several interesting findings regarding baseline DSS. It was notable that DSS was low overall and, in fact, had a negative mean value in women. Age, pulse pressure, and prevalent cardiovascular disease were associated particularly with lower baseline DSS. These CRFs are known to be associated with increased stiffness of the aorta and preserved compliance of peripheral arteries, including the brachial artery.[26] Thus, flow reversal may occur in muscular arteries of the arms and legs during diastole as the lower impedance vasculatures of the heart, brain, and internal organs are perfused with blood stored in the relatively compliant peripheral muscular arteries during systole.[25]

An important issue raised by the present study relates to the potential for atherosclerosis in the brachial artery. Despite the systemic nature of traditional CRFs, atherosclerosis has a predilection for branch points and other regions of disordered SS in the arterial tree.[2] Investigators have attributed this observation to the impact of local SS on endothelial phenotype.[1] In general, laminar SS, which is found in the brachial artery, has favorable effects, whereas stasis, turbulent shear, and local shear gradients activate endothelial cells and induce a proatherogenic phenotype that includes a loss of bioactive NO.[1] If impaired brachial artery FMD indicated local endothelial dysfunction, one might expect that the brachial artery would be susceptible to atherosclerosis. In fact, clinically significant atherosclerosis is rare in the brachial artery, even in patients with advanced coronary or carotid atherosclerosis.[27] Furthermore, in a previous in vitro study, endothelium-dependent dilation was intact in segments of radial artery (which is adjacent to the brachial artery) obtained from patients with advanced coronary artery disease.[28] The present study may help clarify these apparent discrepancies because our data suggest that the observed reductions in hyperemia-induced FMD% in individuals with various CRFs are attributable largely to a reduction in the stimulus for dilation during hyperemia rather than impairment in local endothelial function in the brachial artery.

Our study has several limitations. For example, it remains possible that brachial artery responses to other endothelium-dependent agonists (eg, acetylcholine) are impaired by CRFs, as is the case in the coronary circulation.[5] We have not examined the responses of the conduit brachial artery or forearm resistance vessels to nonendothelium-dependent dilators, although it is important to note that it is not possible to perform such a study in a large community-based setting. In addition, it is possible that the low hyperemic response observed in some participants is insufficient to differentiate the effects of CRFs on local endothelial function as reflected by FMD%. CRFs may be associated more strongly with DSS than FMD% because DSS can be measured with greater reproducibility. Finally, we used a fixed time window after cuff deflation to assess FMD%, which tends to underestimate FMD% because peak dilation timing is variable. These limitations are balanced by several strengths, including the large sample size, which allowed us to evaluate multivariable models with adequate power to detect even modest relationships between CRFs and FMD and the community-based cohort with routine assessment of brachial artery function and CRFs, which minimized potential selection bias. Our study underscores the need for quantitative assessment of flow and SS responses when interpreting brachial artery FMD data. Ultrasound-based study of FMD% is technically difficult and has substantial variability because of the limited resolution of currently available ultrasound systems. It is possible that studies of microvascular function, including evaluation of the hyperemic flow response may provide more reproducible and useful information.[10] Our data suggest that it would be reasonable for all cross-sectional and intervention studies of brachial FMD% to consider including the SS or flow response as a covariate in statistical models. Furthermore, examination of the actual level of mean or DSS or diastolic

flow during hyperemia is preferable to hyperemic-to-baseline ratios because the presence of low baseline flows in the denominator renders such ratios unstable and may obscure the relationship between flow stimulus and FMD% response.

Perspectives

Our findings are consistent with the hypothesis that many CRFs impair brachial artery FMD by reducing the hyperemic stimulus for dilation rather than by impairing endothelial function in the conduit brachial artery. We have shown that variations in baseline and evoked SS were related closely to conventional CRFs, including independent contributions from mean and pulse pressure, obesity, and fasting glucose. These findings have important implications for future studies that examine brachial artery endothelial function and emphasize the need to consider the flow and SS response when interpreting the brachial dilatory response. In addition, these findings are consistent with the hypothesis that local SS plays the predominant role in determining local endothelial function and, by inference, risk for local atherosclerotic lesion development, despite the presence of systemic CRFs.

Acknowledgments

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