The Brachial Artery Remodels to Maintain Local Shear Stress Despite the Presence of Cardiovascular Risk Factors

William B. Chung, Naomi M. Hamburg, Monika Holbrook, Sherene M. Shenouda, Mustali M. Dohadwala, Dellara F. Terry, Noyan Gokce, Joseph A. Vita

Objective—Under physiological conditions, arteries remodel in response to changes in blood flow to maintain local shear stress. Risk factors and developing atherosclerosis may be associated with maladaptive remodeling that produces relatively large arteries with low levels of shear stress. Recent studies have shown that the brachial artery and other peripheral arteries are enlarged in patients with risk factors and cardiovascular disease, and we tested the hypothesis that this finding represents maladaptive remodeling.

Methods and Results—We measured brachial artery diameter and flow by ultrasound and calculated shear stress in a diverse cohort of 1583 subjects (age 53±17 years, 62% male, and 51% with coronary artery disease and/or peripheral arterial disease). In a stepwise linear regression model, age (P<0.001), gender (P<0.001), body mass index (P<0.001), hypertension (P=0.005), and hypercholesterolemia (P=0.02) were associated with larger brachial diameter. Older age was associated with lower shear stress (P<0.01), consistent with maladaptive remodeling. However, body mass index, hypertension, hypercholesterolemia, and prevalent atherosclerosis were associated with proportionate changes in blood flow and no difference in shear stress compared to reference groups, suggesting adaptive remodeling.

Conclusions—These findings suggest that enlargement of the brachial artery in the setting of obesity, hypertension, hypercholesterolemia, and atherosclerosis reflects adaptive remodeling. The results provide further support for the concept that arterial remodeling is an important homeostatic response that is maintained despite the presence of risk factors and developing atherosclerosis. (Arterioscler Thromb Vasc Biol. 2009;29:606-612.)

Key Words: remodeling ■ risk factors ■ atherosclerosis ■ shear stress ■ brachial artery

Long-term changes in arterial blood flow stimulate parallel changes in arterial size. Increased flow stimulates outward remodeling, whereas decreased flow produces a physiological reduction in arterial size. Such adaptive remodeling depends on normal endothelial function and activation of a local and self-limited inflammatory response in the arterial wall. Studies suggest that changes in shear stress at the endothelial surface provide the signal for remodeling. Because shear stress relates inversely to the cube of the lumen radius, an increase in lumen diameter after an increase in flow represents a homeostatic response that tends to restore shear stress toward baseline.

Arterial remodeling contributes to the development and clinical expression of atherosclerosis. As described by Glagov, coronary arteries initially undergo adaptive outward remodeling as atherosclerotic plaques impinge on the arterial lumen, although this mechanism is overwhelmed with increasing plaque burden. Consistent with the idea that remodeling involves local inflammation, proinflammatory risk factors may be associated with excessive arterial remodeling that results in larger arteries with relatively low shear stress. Low shear stress promotes a proatherosclerotic endothelial phenotype, and in the coronary circulation, low shear stress is associated with plaque vulnerability.

Peripheral arteries may also undergo such maladaptive remodeling. Obesity, diabetes mellitus, and other risk factors are associated with larger diameter of the carotid and brachial arteries. Furthermore, larger brachial arterial size is associated with increased incidence of cardiovascular events, suggesting that the stimuli for maladaptive remodeling may be systemic in nature. On the other hand, larger peripheral arteries in the setting of obesity and associated risk factors could reflect adaptive remodeling as blood flow increases to meet the oxygen and nutrient demands of a larger tissue mass. Thus, it remains unclear whether the observed association between risk factors and arterial size reflects adaptive or maladaptive remodeling.

In the present study, we sought to investigate this issue by examining the clinical correlates of brachial artery size and the relation between risk factors and arterial shear stress in a large and diverse cohort of subjects. We hypothesized that risk factors and prevalent atherosclerosis would be associated with maladaptive remodeling as evidenced by larger arterial size and relatively low arterial shear stress.
Methods

Study Participants
We pooled baseline ultrasound and risk factor data from 1583 subjects who had participated in published and unpublished studies of endothelial function at Boston University School of Medicine between 1994 and 2008. The participants in these studies had been identified by review of medical records and by advertisement. Potential subjects were excluded if they had a positive urine pregnancy test, clinical evidence of congestive heart failure, or unstable coronary disease. All participants gave written informed consent, and the Boston Medical Center Institutional Review Board approved all study protocols.

Study Protocol
A standard protocol for assessment of risk factors and measurement of brachial artery diameter and flow has been used in the laboratory since 1994 and has been previously described. Study personnel interviewed subjects and reviewed medical records to identify demographics, medications, ethnicity, and clinical history of coronary artery or peripheral arterial disease, diabetes mellitus, hypertension, family history of premature coronary artery disease, cigarette smoking at any time, and hypercholesterolemia. Blood pressure was measured using an automatic recorder (Dinamap, General Electric Healthcare). Weight measurements and height were used to calculate body mass index. A fasting lipid panel, glucose, and creatinine were measured at the time of study in subsets of 1404, 1117, and 993 subjects, respectively.

For vascular testing, the brachial artery was imaged using high-resolution ultrasound and a linear-array transducer after the subject rested supine in a quiet dark room for at least 10 minutes. Using electrocardiographic triggering, 2-dimensional end-diastolic images and Doppler flow signals were recorded. In a subset of 775 patients, brachial artery images were also obtained 4 minutes after sublingual nitroglycerin (0.4 mg). The nitroglycerin portion of the study was omitted if the participant declined or had previous adverse reactions to nitroglycerin, migraine headaches, severe carotid stenosis, systolic blood pressure of less than 100 mm Hg, or had used sildenafil, tadalafil, or vardenafil within one week of the study.

Brachial artery diameter was measured offline in a blinded manner using commercially available software (Medical Imaging Applications LLC). Baseline flow (ml/min) was calculated using flow velocity measured by ultrasound and vessel cross-sectional area as described previously. Brachial artery shear stress (dynes/cm²) was calculated as 8 μV/diameter, where μ is blood viscosity (assumed to be 0.035 dyne-sec/cm²) and V is brachial velocity (cm/s) at baseline.

Statistical Analysis
Male and female subjects were divided into 3 groups based on sex-specific tertiles of brachial artery diameter. Clinical characteristics of the 3 groups were compared using 1-way analysis of variance for continuous variables and the Chi-square test for categorical variables. Stepwise linear regression was used to identify multivariable correlates of brachial diameter. Candidate variables included age, gender, body mass index, atherosclerosis (coronary artery disease and/or peripheral arterial disease), hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary artery disease, and cigarette smoking. These variables were selected because they had a significant relation with brachial diameter in the univariable analysis (P<0.05). We used categorical risk factors in the primary analysis to maximize the sample size with complete covariate data. In secondary analyses, measured lipids, glucose, and blood pressure values or concurrent medications were included as candidate variables. A similar approach was used to determine the multivariable correlates of postnitroglycerin brachial diameter, which provides a measure of brachial diameter with minimal effect of arterial tone. Finally, analysis of variance was used to calculate adjusted mean values of brachial artery diameter, flow, and shear stress according to presence or absence of atherosclerosis, hypertension, and hypercholesterolemia, level of body mass index (normal, overweight, obese), and tertile of age while adjusting for the other covariates. Analyses were completed using SPSS 12.0.1 (SPSS Inc). Data are reported as mean±SD, unless otherwise specified.

Results

Clinical Characteristics
Table 1 presents the clinical characteristics of the 1583 participants. The cohort was predominantly male with a mean age of 53±17 years (range 18 to 90). There was a high prevalence of risk factors and clinically evident atherosclerosis (coronary artery disease and/or peripheral arterial disease). The brachial artery was free of visible plaque in all subjects.

Risk Factors and Brachial Artery Diameter
Table 1 also displays the prevalence of cardiovascular risk factors according to sex-specific tertiles of resting brachial artery diameter. By design, the proportion of men and women in each sex-specific tertile was the same (62% male). As shown, individuals with the largest brachial arteries were more likely to have a clinical history of cardiovascular risk factors and atherosclerosis. Similarly, participants with the largest brachial arteries were older, had higher body mass index, blood pressure, serum triglycerides, and glucose, and had lower HDL cholesterol levels. As shown in Table 2,
individuals with the largest brachial arteries were more likely to be taking the listed cardiovascular medications.

Table 3 lists the multivariable correlates of brachial artery diameter. In a stepwise model, age, gender, body mass index, prevalent atherosclerosis, hypertension, and hypercholesterolemia were retained as significant correlates. The same variables except hypercholesterolemia remained significant when serum lipids, glucose, and blood pressure were also included as candidate variables. When cardiovascular medications were included as candidate variables, age, gender, atherosclerosis, body mass index, hypertension, and use of antiplatelet agents were significant correlates, but the other medications were not.

**Correlates of Postnitroglycerin Brachial Diameter**

Resting brachial artery diameter measured by ultrasound is influenced by arterial tone in addition to the intrinsic size of the artery. A subset of 775 participants received sublingual nitroglycerin at a dose that produces maximal vasodilation. To investigate the relation of arterial size to risk factors while minimizing the potentially confounding effects of arterial tone, we examined the clinical correlates of postnitroglycerin diameter. As shown in Table 3, the correlates of postnitroglycerin diameter were similar to the correlates of resting brachial diameter, with the exception that clinical history of hypertension was not retained in the model. The similar findings may not be surprising because these two variables are highly correlated ($R=0.94$, $P<0.001$).

**Maladaptive Versus Adaptive Remodeling**

We used resting brachial diameter and arterial flow to calculate arterial shear stress in each subject and reasoned that maladaptive outward remodeling would be associated with lower shear stress, whereas adaptive outward remodeling would lead to a change in diameter without a change in shear stress. This reasoning depends on the assumption that the subjects are in a steady state and had not had a recent change in brachial artery blood flow with insufficient time for remodeling to occur. Table 4 displays adjusted mean values.
for brachial diameter, brachial flow, and calculated shear stress for category of body mass index and for presence or absence of hypertension and hypercholesterolemia. As shown, these factors were associated with higher brachial diameter, but no difference in shear stress, consistent with adaptive outward remodeling. There was a trend ($P = 0.07$) for lower shear stress in patients with hypertension.

In the univariable analysis, atherosclerosis was associated with larger brachial arteries (4.27 ± 0.79 versus 4.04 ± 0.85 mm, $P = 0.001$) and lower shear stress (13.2 ± 8.7 versus 14.8 ± 8.8 dynes/cm², $P = 0.001$). However, as shown in Tables 3 and 4, after adjusting for risk factors the relation became an inverse one, and atherosclerosis was actually associated with smaller adjusted mean diameter. Because blood flow was lower and shear stress was not different, the findings are consistent with adaptive inward remodeling.

In contrast to the risk factors and prevalent atherosclerosis, shear stress did not vary according to age and gender. As shown in Table 5, men had larger arteries, higher flow, and lower shear stress, compared to women ($P < 0.001$ for all). As shown in the Figure, older age was associated with larger brachial arteries (4.35 ± 0.03 versus 3.95 ± 0.04 mm, $P < 0.001$) and lower shear stress (12.9 ± 0.44 versus 15.1 ± 0.53 dynes/cm², $P = 0.01$) for the oldest versus youngest tertile of age, respectively (mean ± SEM adjusted for gender, body mass index, hypertension, hypercholesterolemia, and atherosclerosis), suggesting maladaptive remodeling.

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Mean ± SEM adjusted for age. Subjects with no risk factors also had no history of coronary artery disease or peripheral arterial disease, and body mass index was less than 25 kg/m².

Figure. Displayed are adjusted mean (±SEM) brachial artery diameter, flow, and shear stress according to tertile of age. Means are adjusted for gender, body mass index, and history of atherosclerosis (coronary artery or peripheral arterial disease), hypertension, and hypercholesterolemia. As shown, older age is associated with larger brachial artery diameter and lower arterial shear stress but no difference in flow, consistent with maladaptive remodeling.

Reference group of 115 subjects (47% male, age 32 ± 12 years) with body mass index less than 25.0 kg/m² and no risk factors or clinical history of atherosclerosis. As shown in Table 5, men and women in this reference group had smaller brachial arteries and lower brachial flow, but similar levels of shear stress compared to the rest of the cohort after adjusting for age. This reference shear stress value (14.4 ± 1.0 dynes/cm²) is similar to the level of shear stress observed in patients with individual risk factors and atherosclerosis (Table 4).

Discussion
In this study male sex, older age, higher body mass index, classical cardiovascular risk factors, and coronary or peripheral atherosclerosis were associated with larger brachial
arteries in univariable analyses. Risk reduction medications were also associated with larger arteries, possibly reflecting “confounding by indication.” In stepwise models, age, gender, body mass index, atherosclerosis, and history of hypertension and hypercholesterolemia remained as multivariable correlates of diameter. Several risk factors associated with obesity were not retained in the model after accounting for body mass index, including diabetes mellitus, and serum glucose, triglycerides, and HDL levels.

Despite the larger brachial size, shear stress was not lower in subjects with many of these risk factors. This finding suggests that adaptive remodeling had occurred and argues against our original hypothesis that such factors would be associated with maladaptive remodeling. Indeed, mean brachial artery shear stress in subjects with risk factors was very similar to shear stress in a reference group with no risk factors. Older age, however, was associated with lower shear stress, suggesting maladaptive remodeling. Interestingly, males had substantially lower shear stress compared to women, even after adjusting for other risk factors.

Prior studies have linked cardiovascular risk factors to larger peripheral arterial diameter, and it has been suggested that arterial size might serve as a surrogate for cardiovascular risk. In the Framingham Heart Study, classical risk factors were associated with larger brachial artery diameter, and in multivariable models, the strongest predictors were age, gender, and body mass index. In the Women Ischemia Syndrome Evaluation (WISE) study, brachial artery diameter related to the presence of coronary artery disease. In the Cardiovascular Health Study (CHS), larger brachial diameter predicted cardiovascular events in a cohort of elderly subjects. The size of the carotid artery also relates to the presence of risk factors including age, male gender, body mass index, smoking, and hypertension. The present study extended that prior work by examining brachial diameter after nitroglycerin, which may provide better information about the physical size of the artery without the confounding effects of arterial tone. Importantly, we also examined flow and shear stress to determine whether observed differences in arterial size are attributable to maladaptive remodeling.

Our finding that larger arterial size appears to reflect adaptive remodeling may differ from prior studies that examined stenotic coronary arteries. Indeed, a number of studies have suggested excessive outward remodeling and relatively low shear stress at sites of coronary or carotid atherosclerosis. Low shear stress promotes a proatherosclerotic inflammatory phenotype in endothelial cells, and atherosclerotic lesions tend to develop at sites of low shear stress in the arterial tree. Thus, excessive outward remodeling may perpetuate lesion development and promote plaque vulnerability. Studies with intravascular ultrasound suggest that certain risk factors, particularly hypercholesterolemia, stimulate the remodeling response, and we had hypothesized that the systemic effects of risk factors might also drive maladaptive remodeling in the brachial artery.

There are a number of possible explanations for the apparent differences between studies in the coronary circulation and the present study. The brachial artery is straight, nonbranching, and free of obstructive atherosclerotic lesions and has relatively uniform shear stress that can be estimated from average flow velocity and arterial diameter. In contrast, the coronary arteries have bends and branch points and contain eccentric atherosclerotic lesions that produce marked variation in local shear stress. Thus, the effects of systemic risk factors on the remodeling process may differ in these two vascular beds. On the other hand, the present study allowed us to investigate the effects of risk factors on remodeling in isolation from the effects of local plaque. Our findings are consistent with prior work linking older age and male sex to larger brachial artery diameter and lower shear stress.

The current study suggests that risk factors do not inhibit adaptive remodeling and that the brachial arteries are larger because flow is higher. These findings are consistent with our prior work showing no effect of risk factors on flow-induced remodeling of the ulnar artery after removal of the radial artery in patients undergoing coronary bypass surgery. The findings are also consistent with the original work by Glagov who noted that the remodeling response is initially preserved and maintains lumen size despite the presence of risk factors and developing coronary atherosclerosis.

Why are risk factors associated with higher brachial artery flow? In regard to obesity, higher flow may reasonably be attributed to greater tissue mass in the forearm. It is less clear, however, why hypertension or hypercholesterolemia would lead to higher brachial flow. Body mass index is a poor measure of body fat and muscle distribution, and it is possible that subjects with hypertension and hypercholesterolemia have greater arm tissue mass, even after adjusting for body mass index. Insulin is a vasodilator, and states of insulin resistance are associated with higher baseline flow as well as higher blood pressure and dyslipidemia. Natriuretic peptides also have vasodilator properties, and elevated levels in the setting of risk factors or hypertensive heart disease also might lead to chronically elevated basal forearm flow. Hypertension and other risk factors are also associated with increased stiffness of the central aorta and altered microvascular function, which affects pulsatility, wave reflection, and flow in the brachial artery. We did not measure arm size, serum insulin or natriuretic peptides, or pulsatility in the present study, so additional studies will be required to investigate these and other possible mechanisms.

It is notable that patients with prevalent coronary artery or peripheral arterial disease had larger brachial diameter in the unadjusted analysis, but smaller diameter after adjustment for risk factors. The results were similar for postnitroglycerin diameter. These findings indicate that after taking into account the older age and greater prevalence of risk factors in patients with atherosclerosis, arterial diameter is actually smaller than expected. The smaller adjusted diameter was accompanied by a correspondingly lower arterial flow and no change in shear stress, suggesting that prevalent atherosclerosis did not interfere with remodeling. The explanation for lower flow in atherosclerosis remains unclear, but it is conceivable that patients with atherosclerosis, particularly peripheral arterial disease, might have lower levels of physical activity or reduced tissue mass in the arms leading to a relatively low blood flow. Increased circulating levels of
vasoconstrictors, such as endothelin-1 or thromboxane, might also influence resting forearm blood flow in this setting.43

Our study has a number of limitations. Given the cross-sectional design of our study, we cannot make conclusions about causality and can only speculate about the mechanisms accounting for observations. Our formula to calculate shear stress applies to straight nonbranching arteries, used an assumed value for viscosity that did not consider hematocrit and fibrinogen levels, and did not account for the pulsatile nature of arterial flow. We suggest, however, that these assumptions are reasonable in the brachial artery, and shear stress calculated in this manner has been shown to be clinically relevant in previous studies.5,34 Although external ultrasound provides an accurate measure of lumen size, it did not allow us to assess the thickness of the arterial wall. Many prior studies have focused on the external arterial dimensions when evaluating remodeling, particularly in the presence of an atherosclerotic plaque, but this issue is less of a concern in the lesion-free brachial artery. These limitations are counterbalanced by the large sample size, diverse cohort of subjects, and the standardized ultrasound protocol.

In conclusion, our study provides new insights into the relations between risk factors and arterial remodeling in peripheral arteries. We observed that older age and other cardiovascular risk factors are associated with larger brachial artery size. Older age was associated with lower arterial shear, suggesting maladaptive remodeling. Other risk factors, however, were associated with proportionally higher blood flow and no difference in shear stress, suggesting that larger diameter in these settings represent adaptive remodeling. Our study has a number of limitations. Given the cross-sectional design of our study, we cannot make conclusions about causality and can only speculate about the mechanisms accounting for observations. Our formula to calculate shear stress applies to straight nonbranching arteries, used an assumed value for viscosity that did not consider hematocrit and fibrinogen levels, and did not account for the pulsatile nature of arterial flow. We suggest, however, that these assumptions are reasonable in the brachial artery, and shear stress calculated in this manner has been shown to be clinically relevant in previous studies.5,34 Although external ultrasound provides an accurate measure of lumen size, it did not allow us to assess the thickness of the arterial wall. Many prior studies have focused on the external arterial dimensions when evaluating remodeling, particularly in the presence of an atherosclerotic plaque, but this issue is less of a concern in the lesion-free brachial artery. These limitations are counterbalanced by the large sample size, diverse cohort of subjects, and the standardized ultrasound protocol.

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Sources of Funding
This work was supported by grants from the National Institutes of Health (HL083269, HL083801, HL081587, and HL75795) and the Boston Medical Center General Clinical Research Center (M01RR00533). Dr Hamburg is supported by the Boston University Leadership Program in Vascular Medicine (K12 HL083781). Dr Dohadwala is supported by the Boston University School of Medicine Basic Science Cardiovascular Training Program (T32 HL 07224). Dr Terry is supported by a Paul Beeson Physician Faculty Scholar in Aging Award (K23 AG026754). Dr Gokce is supported by grants from the National Institutes of Health (HL074097 and HL084213).

Disclosures
None.

References


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Arterioscler Thromb Vasc Biol. 2009;29:606-612; originally published online January 22, 2009;
doi: 10.1161/ATVBAHA.108.181495

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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