ORIGINAL RESEARCH

# Vascular Function at Baseline in the Hemodialysis Fistula Maturation Study

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***Background*—**End-stage renal disease is accompanied by functional and structural vascular abnormalities. The objective of this study was to characterize vascular function in a large cohort of patients with end-stage renal disease, using noninvasive physiological measurements, and to correlate function with demographic and clinical factors.

***Methods and Results*—**We analyzed cross-sectional baseline data from the Hemodialysis Fistula Maturation Study, a multicenter prospective observational cohort study of 602 patients with end-stage renal disease from 7 centers. Brachial artery flow- and nitroglycerin-mediated dilation, carotid-femoral and -radial pulse wave velocity, and venous occlusion plethysmography were performed prior to arteriovenous fistula creation. Relationships of these vascular function measures with demographic, clinical, and laboratory factors were evaluated using linear mixed-effects models. Arterial function, as assessed by flow- and nitroglycerin-mediated dilation and carotid-femoral pulse wave velocity, worsened with increasing age and diabetes mellitus. Venous capacitance decreased with diabetes mellitus but not with age. Flow-mediated dilation was higher among patients undergoing maintenance dialysis than for those at predialysis, and a U-shaped relationship between serum phosphorus concentration and flow-mediated dilation was evident. Partial correlations among different measures of vascular function, adjusting for demographic factors, diabetes mellitus, and clinical center, were modest or essentially nonexistent.

***Conclusions*—**Multiple demographic and clinical factors were associated with the functions of vessels of different sizes and types in this large cohort of patients with end-stage renal disease. Low correlations between the different measures, controlling for demographic factors, diabetes mellitus, and center, indicated that these different types of vascular function otherwise vary heterogeneously across patients. **(*J Am Heart Assoc*. 2016;5:e003227 doi: 10.1161/JAHA.116.003227)**

**Key Words:** chronic kidney disease • end-stage renal disease • flow-mediated dilation • nitroglycerin-mediated dilation • pulse wave velocity • vascular function • venous occlusion plethysmography

Patients with end-stage renal disease (ESRD) have a high burden of vascular disease as a result of both traditional risk factors such as hypertension and diabetes mellitus and nontraditional risk factors such as disordered mineral metabolism. Brachial artery flow-mediated dilation (FMD) and pulse wave velocity (PWV) are noninvasive physiological measures of arterial function that provide information about endothelial function and arterial stiffness, respectively.

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Among persons with preserved kidney function, both reduced FMD and increased PWV predict future cardiovascular events.[1,2] Forearm venous occlusion plethysmography (VOP) provides an indirect indication of venous capacitance by measuring the increase in forearm volume in response to outflow obstruction.[3] Venous capacitance, as assessed by VOP, has been associated with hemodialysis arteriovenous fistula (AVF) maturation, a process that requires venous as well as arterial dilation.[4] Although it is well appreciated that ESRD is accompanied by structural and functional alterations in blood vessels, most descriptions of noninvasive physiological measures of vascular function in ESRD populations come from single-center studies that assessed only one type of vascular function.[5–11] It is not known whether the clinical and demographic factors that are associated with vascular function abnormalities among persons with preserved kidney function are also important for ESRD patients. In addition, relationships between different types of vascular function, such as endothelium-dependent and -independent processes, or between functions of different types of vessels, such as elastic arteries, muscular arteries, resistance arterioles, and veins, have not been established in ESRD. It is not known, for example, whether arterial stiffness is accompanied by low venous capacitance after accounting for major systemic factors such as age.

The Hemodialysis Fistula Maturation Study (HFM) was a multicenter prospective cohort study designed to identify predictors and underlying mechanisms of hemodialysis AVF maturation.[12] The study enrolled patients with ESRD undergoing surgical creation of an AVF. Preoperative vascular function studies were performed to determine relationships between underlying vascular function and AVF maturation. This rich data set provides a unique opportunity to examine the determinants of vascular function in ESRD, separate from any linkages to AVF maturation. The objectives of this report were to characterize vascular function in the HFM participants and to describe cross-sectional relationships (1) between vascular function measures and demographic, clinical, and biochemical factors and (2) among the different vascular function measures, adjusted in each case for potential confounding by age, sex, race, and diabetes mellitus status.

# Methods

## Participants

The HFM enrolled 602 patients from 7 centers who underwent creation of an AVF between March 23, 2010, and September 23, 2013. Enrollment required completion of at least 2 of the following 3 sets of studies within 45 days prior to AVF creation: (1) brachial artery FMD followed by nitroglycerin-mediated dilation (NMD) unless contraindicated, (2) carotid-radial (C-R) and carotid-femoral (C-F) PWV, and (3) VOP. Approval for the study was obtained from the institutional review board of each center, and all participants provided informed consent.

## Vascular Function Studies

Vascular function studies used uniform protocols and were performed by study personnel who were trained and certified by the HFM Vascular Function Core at Boston University. Participants fasted for at least 6 hours prior to the studies and refrained from exercise starting at midnight before the studies. When possible, all studies were performed on a single day in the following order: (1) VOP, (2) arterial PWV, (3) brachial artery FMD, and (4) brachial artery NMD. Studies were performed on the arm that was expected to be used for AVF creation unless there was a patent arteriovenous vascular access in that arm. Prior to performing VOP, after a 10-minute period of rest, blood pressure and heart rate were measured using a SunTech 247 device (SunTech Medical). Three measurements of blood pressure and heart rate were obtained, each separated by 1 minute.

### *Brachial artery reactivity*

FMD was measured as an indicator of the endothelium-dependent arterial dilatory response to increased blood flow, and NMD was determined as an indicator of the endothelium-independent arterial dilatory response to nitroglycerin, an exogenous source of nitric oxide. After placement of a custom Hokanson 3.25″×22″ blood pressure cuff with a quick release sphygmomanometer (D.E. Hokanson, Inc.) on the upper arm and 10 minutes of rest in a supine position, a high-resolution linear ultrasound probe (≥7.5 MHz) was used to obtain 2-dimensional images of the brachial artery and pulsed wave Doppler signals. The blood pressure cuff was then inflated to 200 mm Hg or to 50 mm Hg above the systolic blood pressure, whichever value was higher. After 5 minutes of inflation, the cuff was deflated. At 15 seconds after deflation, brachial artery Doppler signals were obtained. The 2-dimensional images gated on the R-wave were obtained 55 to 65 seconds after deflation to determine FMD. Following a 10-minute period of rest in a supine position, 2-dimensional ultrasound imaging of the brachial artery was performed again at the same location used for the measurement of FMD. Nitroglycerin was administered sublingually at a dose of 0.4 mg, and brachial artery ultrasound imaging was repeated 3 minutes later to determine NMD. NMD was not assessed if any of the systolic blood pressure readings were <100 mm Hg, if there was use of a phosphodiesterase type 5 inhibitor within the past 7 days, or if there was a history of migraine headaches or nitroglycerin intolerance.

The 2-dimensional images were used for measurement of brachial artery diameter using customized software, and the Doppler signals were used for determination of flow. Image analysis was performed at the HFM Vascular Function Core facility at Boston University. Resting and hyperemic flow were determined from the Doppler signals. Hyperemic flow is dependent on ischemia-induced dilation of resistance arterioles and is mediated in part by nitric oxide.

### *C-R and C-F arterial PWV*

PWV was measured using the SphygmoCor device (Atcor Medical) as an assessment of stiffness of the aorta (C-F PWV) and the upper extremity arteries (C-R PWV). The C-F distance was computed as the distance from the sternal notch to the femoral pulse minus the distance from the sternal notch to the carotid pulse. The C-R distance was computed as the distance from the sternal notch to the radial pulse minus the distance from the sternal notch to the carotid pulse. The pulse waveforms were recorded using applanation tonometry at the carotid followed by the radial sites for the C-R PWV determination and at the carotid followed by the femoral sites for C-F PWV determination. Waveform acquisition was repeated if the automated, device-determined standard deviation for a set of 10 waveforms was >10%. The QRS complex from electrocardiogram leads served as the reference for the origin of the pulse waveform. Pulse wave velocities are expressed as meters per second.

### *Venous occlusion plethysmography*

VOP was performed to assess the capacitance of the veins in the upper extremity. Participants were placed in a supine position with the arm supported and elevated above the level of the heart. The Hokanson EC5 strain-gauge plethysmography device with NIVP3 software was used for waveform acquisition and analysis (D.E. Hokanson, Inc). A strain gauge of appropriate size was placed around the forearm at the position of greatest diameter to measure change in forearm circumference. An SC10D arm cuff (D.E. Hokanson, Inc) placed on the upper arm was inflated for 3 minutes to the designated pressure and then deflated using an automated rapid inflator device. Waveforms were acquired while the cuff was inflated and for 5 seconds after deflation. The procedure was performed at cuff inflations to 20, 30, 40, 50, and 60 mm Hg in succession. The relative change in forearm volume after cuff inflation, expressed as milliliter increase per 100 mL of forearm volume (mL/100 mL), was determined at each cuff pressure; the slope of its regression on cuff pressure, termed "capacitance slope," is taken as the principal measure of venous capacitance. This is expressed as the additional fractional expansion of forearm volume (mL/100 mL) per 10-mm Hg increase in cuff pressure and thus in units Δ(mL/100 mL)/10 mm Hg. The mean relative increase in forearm volume over the 5 cuff pressures (in mL/100 mL) is also described. The maximum venous outflow (mL/100 mL forearm volume per minute) was also recorded after deflation from each cuff pressure. As with capacitance, the slope of its regression on venous pressure, termed "maximum venous outflow slope" and reported as Δ(mL/100 mL per minute)/10 mm Hg, is taken as the principal indicator of maximum venous outflow. The mean maximum relative venous outflow over the 5 cuff pressures (in mL/100 mL per minute) is also described.

## Statistical Methods

In a formal statistical analysis plan, 7 primary and 11 additional vascular function variables (Table 1) were preselected for descriptive summarization in relation to age, sex,

**Table 1.** Vascular Function Measures and Potential Correlates Examined

| Primary Vascular Function Measures | Additional Vascular Function Measures | Potential Correlates |
|---|---|---|
| *Brachial Artery Dilation* | *Brachial Artery Dilation* | Age |
| FMD% | Baseline artery diameter | Sex |
| Hyperemic velocity | Resting velocity | Black vs other race |
| NMD% | Absolute artery dilation | Diabetes |
| *PWV* | Hyperemic velocity-adjusted FMD | Vascular disease* |
| Carotid-femoral PWV | *PWV* | Systolic blood pressure |
| Carotid-radial PWV | Central systolic blood pressure | Diastolic blood pressure |
| *VOP* | Central diastolic blood pressure | Serum albumin |
| Venous CAP slope | Central pulse pressure | Serum calcium |
| MVO slope | Augmentation index | Serum phosphorus |
| | *VOP* | Body mass index |
| | Mean CAP† | Cigarette smoking |
| | Mean MVO‡ | Dialysis treatment |
| | Forearm volume | |

CAP indicates capacitance; FMD, flow-mediated dilation; FMD%, flow-mediated dilation expressed as percent change in artery diameter from baseline; MVO, maximum venous outflow; NMD, nitroglycerin-mediated dilation; NMD%, nitroglycerin-mediated dilation expressed as percent change in artery diameter from baseline; PWV, pulse wave velocity; VOP, venous occlusion plethysmography.

*History of any of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty, congestive heart failure, cardiac arrhythmias or conduction problems, stroke, transient ischemic attack, carotid endarterectomy, carotid artery angioplasty, lower extremity arterial bypass surgery or angioplasty, nontraumatic amputation, and claudication.

†Averaged over the CAP measurements obtained at cuff pressures 20, 30, 40, 50, and 60 mm Hg.

‡Averaged over the MVO measurements obtained at cuff pressures 20, 30, 40, 50, and 60 mm Hg.

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**Table 2.** Primary Vascular Function Measures by Age, Sex, Race, and Diabetes Mellitus Status, Directly Adjusted Individually for Clinical Center*

| Measure | Age, y | | | | | Sex | | Black Race | | Diabetes | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤40 | 40–49 | 50–59 | 60–69 | ≥70 | Female | Male | Yes | No | Yes | No |
| Brachial artery dilation | | | | | | | | | | | |
| FMD% | 6.0 (1.2) | 5.0 (1.6) | 4.5 (1.7) | 4.2 (1.7) | 3.3 (1.2) | 5.5 (1.9) | 4.3 (1.7) | 4.1 (1.8) | 5.0 (1.8) | 3.7 (1.5) | 5.8 (2.1) |
| Hyperemic velocity, cm/s | 102.8 (12.3) | 99.6 (11.3) | 79.8 (12.9) | 72.8 (12.2) | 72.0 (7.2) | 78.4 (15.8) | 84.0 (12.5) | 79.2 (13.2) | 87.7 (13.1) | 80.2 (12.2) | 87.8 (14.6) |
| NMD% | 9.4 (2.4) | 9.4 (2.6) | 7.8 (2.4) | 5.7 (1.9) | 4.3 (1.4) | 9.6 (2.7) | 6.7 (2.2) | 7.1 (2.5) | 7.5 (2.4) | 6.3 (2.2) | 9.0 (2.6) |
| Arterial PWV | | | | | | | | | | | |
| Carotid-femoral PWV, m/s | 8.31 (0.58) | 9.28 (0.79) | 10.59 (1.12) | 10.89 (1.05) | 12.02 (1.02) | 10.00 (1.05) | 10.43 (1.08) | 10.17 (1.08) | 10.70 (1.12) | 11.13 (1.10) | 9.27 (0.93) |
| Carotid-radial PWV, m/s | 9.13 (0.57) | 9.14 (0.64) | 8.83 (0.59) | 8.93 (0.65) | 8.82 (0.60) | 8.60 (0.52) | 9.09 (0.63) | 8.96 (0.64) | 8.54 (0.60) | 9.04 (0.64) | 8.84 (0.61) |
| Venous occlusion plethysmography | | | | | | | | | | | |
| CAP slope Δ (mL/100 mL)/10 mm Hg | 0.58 (0.17) | 0.47 (0.08) | 0.50 (0.10) | 0.51 (0.14) | 0.52 (0.09) | 0.49 (0.09) | 0.52 (0.14) | 0.49 (0.11) | 0.52 (0.12) | 0.47 (0.10) | 0.56 (0.14) |
| MVO slope Δ (mL/100 mL/min)/ 10 mm Hg | 4.38 (1.08) | 3.55 (0.71) | 3.63 (1.01) | 3.69 (1.12) | 3.18 (0.61) | 3.51 (0.85) | 3.82 (1.06) | 3.73 (0.82) | 3.65 (1.01) | 3.43 (0.98) | 4.07 (1.00) |

Data are shown as mean (SE). CAP indicates capacitance; FMD%, flow-mediated dilation expressed as percent change in artery diameter from baseline; MVO, maximum venous outflow; NMD%, nitroglycerin-mediated dilation expressed as percent change in artery diameter from baseline; PWV, pulse wave velocity.

*Values for age–sex–diabetes mellitus–clinical center combinations with ≤2 patients were smoothed by imputation with fitted values from a fixed-effects model with additive clinical center effects and a saturated model for the other variables, minimally reduced if necessary to achieve an identifiable model. Prior to such modeling, cells for each combination were initially adjusted for the variable omitted from that combination (ie, race for the age–sex–diabetes mellitus combinations) by weighting the levels of the omitted variable uniformly by their proportions in the full Hemodialysis Fistula Maturation Study sample.

**Table 3.** Differences in Vascular Function Measures With Age, Sex, Black Race, and Diabetes Mellitus, Adjusted for Clinical Center, From Joint Mixed Multiple Linear Regression Models

| | Age (Per Decade) | | | Male | | | Black Race | | | Diabetes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Measure | Estimate | SE | *P* Value | Estimate | SE | *P* Value | Estimate | SE | *P* Value | Estimate | SE | *P* Value |
| Brachial artery dilation | | | | | | | | | | | | |
| FMD% | −0.38 | 0.15 | 0.013 | −0.78 | 0.39 | 0.047 | −0.50 | 0.38 | 0.19 | −2.00 | 0.40 | <0.0001 |
| Allometrically adjusted FMD% | −0.08 | 0.13 | 0.53 | 1.26 | 0.34 | 0.0007 | 0.08 | 0.33 | 0.82 | −1.80 | 0.36 | <0.0001 |
| Hyperemic velocity, cm/s | −8.37 | 1.00 | <0.0001 | −3.63 | 2.67 | 0.18 | −10.70 | 2.70 | 0.0001 | −4.17 | 2.74 | 0.13 |
| NMD% | −1.10 | 0.20 | <0.0001 | −3.20 | 0.60 | <0.0001 | −0.63 | 0.57 | 0.27 | −2.60 | 0.60 | <0.0001 |
| Allometrically adjusted NMD% | −0.64 | 0.17 | 0.0002 | 0.28 | 0.49 | 0.57 | 0.15 | 0.46 | 0.73 | −2.40 | 0.45 | <0.0001 |
| Arterial PWV | | | | | | | | | | | | |
| Carotid-femoral PWV, m/s | Age, sex, and race interact with diabetes mellitus. Sex and age interact among patients both with and without diabetes mellitus. *P*<0.0001 for diabetes mellitus main effect; *P*<0.0001 for sex by race interaction in diabetes mellitus strata; *P*=0.003 for linear age; *P*=0.008 for nonlinear age trend.* | | | | | | | | | | | |
| Carotid-radial PWV, m/s | −0.03 | 0.06 | 0.63 | 0.52 | 0.17 | 0.0024 | 0.54 | 0.17 | 0.0013 | 0.31 | 0.16 | 0.054 |
| Venous occlusion plethysmography | | | | | | | | | | | | |
| CAP slope Δ(mL/100 mL)/10 mm Hg | 0.05 | 0.07 | 0.52 | 0.17 | 0.18 | 0.36 | −0.29 | 0.18 | 0.11 | −0.41 | 0.17 | 0.021 |
| MVO slope Δ(mL/100 mL/min)/10 mm Hg | −0.04 | 0.07 | 0.52 | 0.35 | 0.17 | 0.036 | −0.14 | 0.17 | 0.41 | −0.27 | 0.16 | 0.09 |

CAP indicates capacitance; FMD%, flow-mediated dilation expressed as percent change in artery diameter from baseline; MVO, maximum venous outflow; NMD%, nitroglycerin-mediated dilation expressed as percent change in artery diameter from baseline; PWV, pulse wave velocity.
*See Figure 1 for illustration of interactions.

race, and self-reported diabetes mellitus status. The primary variables were correlated with each other and with preselected clinical factors, controlling for these 4 variables (Table 1).

FMD and NMD are expressed as the postischemia and postnitroglycerin percentage changes (FMD% and NMD%), respectively, in brachial artery diameter. Recent papers have argued that diameter change relative to baseline diameter, as in FMD% and NMD%, does not properly standardize arterial dilation to the size of the patient and artery and advocate alternative allometrically adjusted measures.[13–15] To see if such allometric adjustment materially affected results, we modeled 2 suggested alternatives to each of FMD% and NMD %, both formed from regression of log(poststimulus diameter) on log(prestimulus diameter): (1) the patient's residual from this regression[14] and (2) the ratio of the patient's poststimulus to prestimulus diameter after first exponentiating the latter by the estimated regression coefficient.[14]

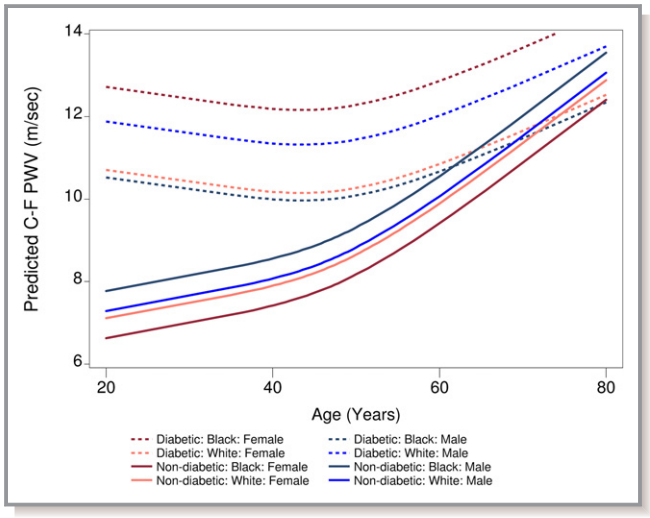


**Figure 1.** Trends of fitted C-F PWV means by age for combinations of sex, black race, and diabetes mellitus across Hemodialysis Fistula Maturation Study clinical centers. C-F indicates carotid-femoral, PWV, pulse wave velocity.

For all vascular function variables studied, we used a modified direct-adjustment procedure to estimate means of each variable in strata formed separately by age (<40, 40–49, 50–59, 60–69, and ≥70 years), sex, black versus other race, and prevalent diabetes and by age–sex–race and age–sex–diabetes mellitus combinations, adjusted to a population equally distributed across clinical sites.[16] For the 2 sets of 3-factor strata estimates, we used a model with clinical sites as fixed blocks and all 3-way interactions of age, sex, race, and diabetes mellitus (or a minimally further reduced model if needed) to impute the site-specific values required by the direct adjustment approach for 3-factor combinations that were absent at specific clinical sites and to smooth site-specific means of combinations with ≤2 patients at ≥1 site.

**Table 4.** Differences in Brachial Artery Dilation Measures Associated With Prespecified Baseline Predictors, Adjusted for Clinical Center, Age, Sex, Black Race, and Diabetes Mellitus, From Mixed Multiple Linear Regression Models

| | FMD% | | | Hyperemic Velocity, cm/s | | | NMD% | | |
|---|---|---|---|---|---|---|---|---|---|
| | Estimate | SE | *P* Value | Estimate | SE | *P* Value | Estimate | SE | *P* Value |
| BMI, per kg/m$^2$ | −0.03 | 0.02 | 0.22 | 0.15 | 0.17 | 0.38 | −0.06 | 0.04 | 0.15 |
| Systolic BP, per 10 mm Hg | −0.07 | 0.08 | 0.38 | 0.12 | 0.05 | 0.03 | −0.41 | 0.12 | 0.001 |
| Diastolic BP, per 10 mm Hg | 0.04 | 0.14 | 0.77 | 0.32 | 0.09 | 0.0003 | −0.01 | 0.21 | 0.95 |
| Serum albumin, per g/dL | −0.30 | 0.31 | 0.34 | 4.05 | 2.13 | 0.06 | 0.17 | 0.46 | 0.72 |
| Serum calcium, per mg/dL | −0.04 | 0.23 | 0.88 | 3.14 | 1.54 | 0.04 | 0.29 | 0.31 | 0.36 |
| Serum phosphorus, per mg/dL | Overall *P*=0.017, nonlinearity *P*=0.010* | | | 0.98 | 0.86 | 0.26 | −0.30 | 0.18 | 0.10 |
| History of vascular disease† | −0.94 | 0.38 | 0.02 | −5.04 | 2.72 | 0.07 | −1.23 | 0.58 | 0.07 |
| Cigarette use past 12 months | −0.80 | 0.43 | 0.06 | −1.69 | 2.93 | 0.56 | −0.51 | 0.63 | 0.42 |
| Maintenance dialysis | 1.20 | 0.40 | 0.002 | −4.46 | 2.63 | 0.09 | 0.10 | 0.58 | 0.87 |

BMI indicates body mass index; BP, blood pressure, FMD%, flow-mediated dilation expressed as percent change in artery diameter from baseline; NMD%, nitroglycerin-mediated dilation expressed as percent change in artery diameter from baseline.

*See Figure 2.

†History of any of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty, congestive heart failure, cardiac arrhythmias or conduction problems, stroke, transient ischemic attack, carotid endarterectomy, carotid artery angioplasty, lower extremity arterial bypass surgery or angioplasty, nontraumatic amputation, and claudication.

Linear mixed-effects statistical models with random effects of clinical sites and fixed effects of age, sex, race, and diabetes mellitus were fitted to each of the 7 primary vascular function and 4 alternative allometrically adjusted measures. A stagewise backward elimination procedure was used, with models successively tested for classes of interactive and nonlinear effects, potentially allowing recognition of such effects if strong, and essentially penalizing complexity and controlling overall type 1 statistical error from multiple testing. The effects of age, sex, race, and diabetes mellitus on each vascular function variable were then estimated and tested while controlling simultaneously for the other 3. Effects of the additional potential demographic and clinical baseline correlates of vascular function were similarly examined by incorporation into the age, sex, race, and diabetes mellitus model reached by this reduction process. These variables were retained in all models, regardless of statistical significance, to adjust for any potential confounding by these factors. The examination of each continuous predictor included an initial test for nonlinearity.

Statistical associations among the vascular function measures were assessed, controlling for clinical site, age, sex,

**Table 5.** Differences in Arterial Pulse Wave Velocity Associated With Prespecified Baseline Predictors, Adjusted for Clinical Center, Age, Sex, Black Race, and Diabetes Mellitus, From Mixed Multiple Linear Regression Models

| | Carotid-Femoral PWV | | | Carotid-Radial PWV | | |
|---|---|---|---|---|---|---|
| | Estimate | SE | *P* Value | Estimate | SE | *P* Value |
| BMI, per kg/m$^2$ | −0.01 | 0.02 | 0.48 | −0.035 | 0.012 | 0.003 |
| Systolic BP, per 10 mm Hg | 0.34 | 0.05 | <0.0001 | 0.22 | 0.03 | <0.0001 |
| Diastolic BP, per 10 mm Hg | 0.32 | 0.08 | <0.0002 | 0.52 | 0.05 | <0.0001 |
| Serum albumin, per g/dL | 0.06 | 0.18 | 0.74 | 0.04 | 0.13 | 0.77 |
| Serum calcium, per mg/dL | −0.13 | 0.12 | 0.28 | −0.09 | 0.09 | 0.31 |
| Serum phosphorus, per mg/dL | 0.11 | 0.08 | 0.15 | 0.04 | 0.05 | 0.43 |
| History of vascular disease* | 0.47 | 0.26 | 0.07 | −0.14 | 0.17 | 0.40 |
| Cigarette use past 12 months | −0.27 | 0.27 | 0.33 | 0.03 | 0.18 | 0.86 |
| Maintenance dialysis | −0.39 | 0.27 | 0.16 | 0.32 | 0.17 | 0.06 |

BMI indicates body mass index; BP, blood pressure; PWV, pulse wave velocity.

*History of any of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty, congestive heart failure, cardiac arrhythmias or conduction problems, stroke, transient ischemic attack, carotid endarterectomy, carotid artery angioplasty, lower extremity arterial bypass surgery or angioplasty, nontraumatic amputation, and claudication.

**Table 6.** Differences in Venous Occlusion Plethysmography Measures Associated With Prespecified Baseline Predictors, Adjusted for Clinical Center, Age, Sex, Black Race, and Diabetes Mellitus, From Mixed Multiple Linear Regression Models

| | CAP Slope, Δ(mL/100 mL)/10 mm Hg | | | MVO Slope, Δ(mL/100 mL/min)/10 mm Hg | | |
|---|---|---|---|---|---|---|
| | Estimate | SE | *P* Value | Estimate | SE | *P* Value |
| BMI, per kg/m$^2$ | −0.067 | 0.011 | <0.0001 | −0.455 | 0.103 | <0.0001 |
| Systolic BP, per 10 mm Hg | 0.021 | 0.036 | 0.56 | 0.039 | 0.033 | 0.25 |
| Diastolic BP, per 10 mm Hg | 0.007 | 0.061 | 0.91 | 0.041 | 0.055 | 0.45 |
| Serum albumin, per g/dL | −0.164 | 0.140 | 0.24 | −3.066 | 1.300 | 0.02 |
| Serum calcium, per mg/dL | −0.099 | 0.098 | 0.31 | −0.946 | 0.894 | 0.29 |
| Serum phosphorus, per mg/dL | 0.114 | 0.054 | 0.04 | 0.929 | 0.509 | 0.07 |
| History of vascular disease* | −0.097 | 0.176 | 0.60 | 2.98 | 1.66 | 0.079 |
| Cigarette use past 12 months | 0.100 | 0.187 | 0.59 | −1.041 | 1.763 | 0.56 |
| Maintenance dialysis | 0.115 | 0.185 | 0.53 | 2.79 | 1.74 | 0.11 |

BMI indicates body mass index; BP, blood pressure.
*History of any of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty, congestive heart failure, cardiac arrhythmias or conduction problems, stroke, transient ischemic attack, carotid endarterectomy, carotid artery angioplasty, lower extremity arterial bypass surgery or angioplasty, nontraumatic amputation, and claudication.

black versus other race, and diabetes mellitus, by pairwise Pearson correlations of the respective residuals of each component from the primary adjustment models developed above.

Analyses were restricted to participants for whom the variables involved were measured, without imputation of missing data. A statistical analysis appendix (Data S1) provides further details of the adjustment and modeling processes. Except as otherwise noted, the criterion for statistical significance was $P<0.05$ and was met by the associations reported.

## Results

Baseline characteristics of all 602 HFM participants and the subgroups with each vascular function test are shown in Table S1. For the full cohort, the mean age was ≈55 years, 44% of the participants were black, and 59% had diabetes mellitus. At the time of AVF creation, 64% were receiving maintenance dialysis. The most frequent reasons for non-completion of each vascular function study were as follows: (1) for FMD, the study was rejected by the core because of technical flaws (5.5%); (2) for NMD, contraindication to nitroglycerin administration was present (9.6%) or the study was rejected by the core because of technical flaws (5.7%); (3) for PWV, technical data capture difficulties were present due to atrial fibrillation or body habitus (10.5%) or standard deviation ≤10% could not be obtained for a set of 10 pulse waveforms (9.8%); and (4) for VOP, technical or logistical difficulties were present at the clinical center (2%). For each vascular function test, baseline characteristics of participants who completed the test were similar to those of the full cohort (Table S1).

Tables 2 and S2 show the primary and additional center-adjusted vascular function measurements, respectively, stratified individually by age, sex, race, and diabetes mellitus, each of which has been found in other populations to be associated with FMD or PWV. Tables S3 and S4 show analogous results for the full set of vascular function measurements but jointly stratified by age, sex, and race (Table S3) and by age, sex, and diabetes mellitus (Table S4). In linear mixed models controlling for clinical site, age, sex, race, and diabetes mellitus (Table 3), increased age was associated with lower hyperemic velocity, FMD%, and NMD% and higher C-F PWV; male sex was associated with lower FMD%, lower NMD%, higher C-R PWV, and higher maximum venous outflow slope. Black race was associated with lower hyperemic velocity and higher C-R PWV, and diabetes mellitus was associated with lower FMD, NMD, and venous capacitance slope and higher C-F PWV and was marginally significantly associated with higher C-R PWV. As illustrated in Figure 1, for C-F PWV, there were interactions between diabetes mellitus and age, sex, and race. C-F PWV, for example, increased with age but was higher among younger patients with diabetes mellitus than in older patients without diabetes mellitus and was higher among female than male black patients with diabetes mellitus but lower in female patients in other subgroups. The relationship between C-F-PWV and age appeared nonlinear, steepening at ≈45 years. Allometric adjustment (Table 3) for FMD% removed the age-related decline and a trend to lower values among black patients and reversed the male–female difference. For NMD%, allometric adjustment attenuated the age-related decline by 42% and removed both the effect of sex and the trend to lower values among black patients. Allometric adjustment had only minimal effects on diabetes-associated reductions for FMD% and NMD%.

Additional factors that were hypothesized to affect vascular function were evaluated for associations with each of the vascular function tests in models incorporating age, sex, race, and diabetes mellitus (Tables 4 through 6). For FMD, clinical history of vascular disease and dialysis treatment were associated with lower and higher FMD%, respectively, and the relationship with serum phosphorus was U-shaped with higher FMD% at low serum phosphorus concentrations and at high concentrations (Figure 2). For hyperemic velocity, both systolic and diastolic brachial artery blood pressures were associated with higher ischemia-induced velocity, and for NMD, systolic brachial artery blood pressure was associated with lower nitroglycerin responsiveness. Relationships between FMD% and both dialysis treatment and phosphorus persisted with allometric adjustment, as did the relationship between NMD% and systolic blood pressure. Allometric adjustment converted an association of vascular disease history with reduced NMD% from marginally nonsignificant ($P$=0.07) to marginally statistically significant ($P$=0.04) (Table S5). For PWV, systolic and diastolic blood pressures were both associated with higher C-F and C-R PWV, and body mass index was associated with lower C-R PWV but not with C-F PWV. For the VOP measures, higher body mass index was associated with lower capacitance and maximum outflow slopes, higher serum albumin was associated with lower maximum outflow slope, and higher serum phosphorus was associated with higher venous capacitance slope and marginally nonsignificantly associated with higher maximum venous output slope.

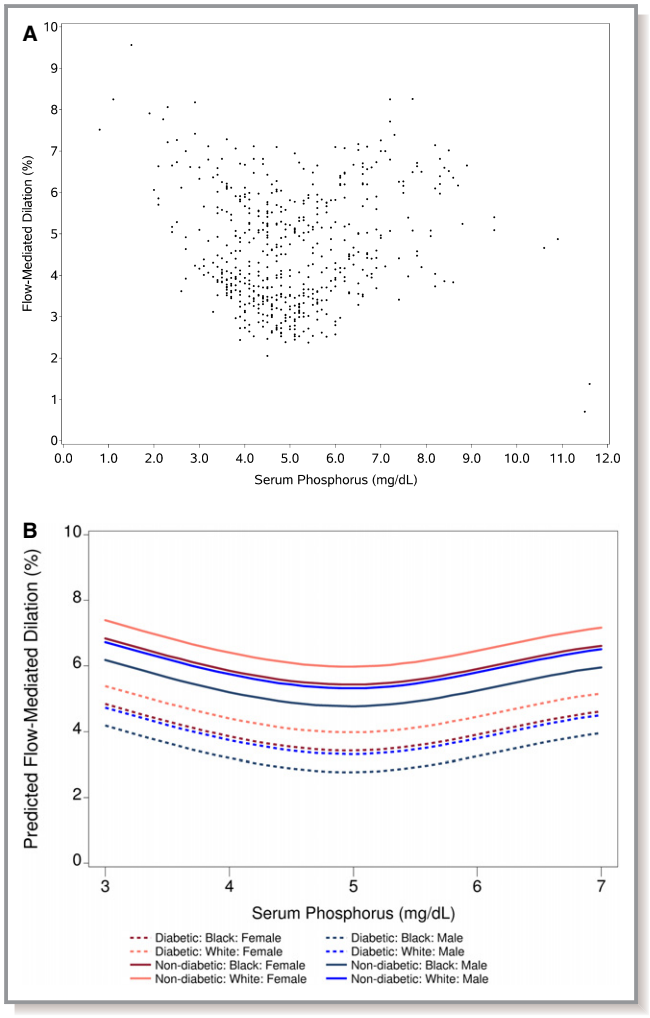


**Figure 2.** Relationship of FMD% to baseline phosphorus. A, Scatterplot of raw data for FMD% and phosphorus at baseline. B, Fitted mean phosphorus values for a mixed statistical model for FMD% in which the relationship of FMD% to serum phosphorus is additively adjusted for Hemodialysis Fistula Maturation Study clinical centers and age, sex, race, and diabetes mellitus at baseline. Lines connect predicted means for each age–sex–race combination. FMD indicates flow-mediated dilation expressed as percent change in artery diameter from baseline.

Partial correlations between different vascular function studies are shown in Table 7. After controlling for demographic factors and diabetes mellitus, relationships of reasonable magnitude were evident for (1) FMD% and NMD% ($R$=0.503, $P$<0.0001) and (2) venous capacitance and maximum venous outflow slopes ($R$=0.671, $P$<0.0001). There were statistically significant but modest correlations between C-F and C-R PWV ($R$=0.196, $P$<0.0001) and between C-F PWV and NMD% ($R$=0.167, $P$=0.0027). There were no apparent relationships between venous capacitance or maximum outflow slopes and any of the measures of arterial function or between measures of brachial artery dilation (FMD or NMD) and PWV.

## Discussion

We performed a comprehensive assessment of vascular function in a large cohort of patients who were being treated with hemodialysis or were anticipated to begin hemodialysis within 3 months. The assessment included evaluation of arteries of different sizes and types as well as the venous system. Some, but not all, attributes that have been associated with impairment in vascular function in populations without chronic kidney disease were similarly associated with vascular functional impairment in our ESRD cohort. Conversely, some of the associations we identified have not been described previously in other populations. Of note, after controlling for the contributions of age, sex, black race, diabetes mellitus, and clinical center, we found only modest correlations among the major categories of vascular function measurements, indicating that the different types of vascular function vary relatively autonomously after accounting for these case-mix factors. Overall, in comparison with cohorts without ESRD, arterial function in the HFM cohort was poor with low FMD and NMD and high C-F PWV, indicating substantial impairments in endothelial function, nitric oxide responsiveness, and arterial compliance, respectively.[17–20]

**Table 7.** Partial Pearson Correlations Between Primary Vascular Function Measures Controlling for Clinical Center, Age, Sex, Black Race, and Diabetes Mellitus

| Variable | Hyperemic Velocity | NMD% | C-F PWV | C-R PWV | CAP Slope | MVO Slope |
|---|---|---|---|---|---|---|
| FMD% | 0.150, $P$=0.0027, n=494 | 0.503, $P$<0.0001, n=421 | −0.076, $P$=0.14, n=382 | 0.080, $P$=0.12, n=383 | −0.033, $P$=0.22, n=517 | 0.048, $P$=0.51, n=517 |
| Hyperemic velocity | — | 0.163, $P$=0.0007, n=412 | 0.039, $P$=0.81, n=376 | 0.020, $P$=0.63, n=377 | 0.101, $P$=0.013, n=504 | 0.062, $P$=0.24, n=504 |
| NMD% | — | — | −0.167, $P$=0.0027, n=321 | 0.026, $P$=0.65, n=321 | −0.014, $P$=0.65, n=434 | 0.039, $P$=0.70, n=434 |
| C-F PWV | — | — | — | 0.196, $P$<0.0001, n=420 | −0.014, $P$=0.42, n=420 | 0.038, $P$=0.56, n=420 |
| C-R PWV | — | — | — | — | 0.020, $P$=0.68, n=421 | 0.038, $P$=0.50, n=421 |
| CAP slope | — | — | — | — | — | 0.671, $P$<0.0001, n=569 |

CAP indicates capacitance; C-F, carotid-femoral; C-R, carotid-radial; NMD%, nitroglycerin-mediated dilation expressed as percent change in artery diameter from baseline; MVO, maximum venous outflow; NMD%, nitroglycerin-mediated dilation expressed as percent change in artery diameter from baseline; PWV, pulse wave velocity.

The relationships between demographic factors and brachial artery reactivity in the HFM participants were similar to those identified in studies of persons with preserved kidney function. In the absence of allometric adjustment, increased age and male sex were associated with lower FMD and NMD in our cohort, as in other populations.[21,22] In addition, as previously reported, FMD% was higher in men than in women after incorporation of allometric adjustment.[14] Although black race was associated with lower hyperemic velocity, we found no relationship between black race and FMD to NMD; this finding differs from a previous study of a cohort without chronic kidney disease in which black race was associated with higher NMD.[23] Among the clinical factors we evaluated, diabetes mellitus was associated with lower FMD and NMD, similar to many studies of other populations.[24,25] The finding that FMD was greater among those receiving treatment with maintenance hemodialysis than in those who had not yet initiated dialysis is consistent with dialytic removal of mediators of endothelial dysfunction and, importantly, suggests that endothelial function is modifiable in this patient population. The largely U-shaped relationship that we observed between serum phosphorus and FMD, with higher FMD% at both low and high phosphorus concentrations, has not been reported in other cohorts. Higher FMD at low phosphorus concentrations is consistent with the generally accepted view that phosphorus has deleterious effects on the vasculature, at least in part by promoting calcification.[26,27] It is not clear, however, why a benefit of low phosphorus was not also evident for NMD or PWV, each of which has more obvious dependence than FMD on vessel wall structure, or why FMD would be better at markedly elevated, compared with moderately elevated, phosphorus levels. Adjustment by dialysis status did not notably alter the shape of the FMD–phosphorus relationship, suggesting that the observed relationship was not simply a reflection of different phosphorus concentrations in patients before and after initiation of maintenance dialysis.

The associations of C-F PWV with age, diabetes mellitus, and both systolic and diastolic blood pressures observed in this study are consistent with well-established risk factors for aortic vascular stiffness[28,29]; however, the interaction of age and diabetes in our cohort, with a greater impact of diabetes mellitus at younger versus older ages, has not been highlighted in cohorts without chronic kidney disease. Our finding may reflect greater severity of manifestations of diabetes mellitus, including diabetes-associated vascular disease, among diabetic patients who develop ESRD at younger ages. In contrast to C-F PWV, we found no association of age and only a borderline statistically non-significant association of diabetes mellitus with higher C-R PWV. Our finding of different risk factors for elevated C-F and C-R PWV is consistent with the results of Pannier et al, who measured C-F and C-R PWV in 305 patients with ESRD and found pulse pressure to be the only factor associated with C-R PWV, whereas age, diabetes mellitus, pulse pressure, smoking, and low-density lipoprotein cholesterol were each associated with C-F PWV.[30] In the population without chronic kidney disease, increases in stiffness associated with aging are greater for the aorta than for peripheral arteries[31]; a similar pattern could underlie the absence of a detectable relationship between C-R PWV and age in the HFM cohort.

Little is known about determinants of venous function in either the presence or absence of chronic kidney disease. The inverse association between serum albumin concentration

and venous outflow may relate to the effects of albumin on blood viscosity. The inverse associations of body mass index with venous capacitance slope and maximum venous outflow may underlie, in part, previously reported associations between obesity and AVF failure.[32,33]

The absence of relationships among different types of vascular function, after adjustment for demographic factors and diabetes mellitus, indicates heterogeneity in patterns of vascular function. The finding that partial associations of each of the arterial function measures with venous function were nonsignificant or negligible is particularly striking.

Our study has limitations. Because participants were required to complete only 2 of the 3 groups of vascular function tests (brachial artery reactivity, PWV, and VOP), missing NMD and PWV data limit the precision of estimates and the power to confirm their associations with possible correlates. Although the similar characteristics of test completers and the full cohort (Table S1) do not suggest this, possible nonresponse bias is also a concern in principle. The lack of normative values for the vascular function studies that we conducted limits comparisons between the HFM cohort and persons with preserved kidney function. Our assessment of arterial stiffness was restricted to PWV and did not include direct assessments of arterial distensibility. Finally, cross-sectional data cannot support causal inferences.

Our study also has a number of strengths. The sample size is substantially larger than most previous studies of vascular function in advanced chronic kidney disease, and the array of vascular studies performed is more comprehensive. The measurements were performed at multiple centers using uniform protocols and central evaluation and quality control of the brachial artery ultrasound images. Consideration of allometric scaling in sensitivity analyses allowed us to determine that most FMD and NMD findings were qualitatively similar if the degree of dilation was allometrically standardized to body size and brachial artery diameter.

In summary, this study provides the cross-sectional results of a comprehensive assessment of vascular function in a large cohort of patients with ESRD, describes the relationships between these tests, and identifies demographic and clinical factors associated with each.

## Appendix

### Contributors

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## Disclosures

None.

## References

1. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014;15:736–746.
2. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier

B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014;63:636–646.

3. Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. *Br J Clin Pharmacol*. 2001;52:631–646.
4. van der Linden J, Lameris TW, van den Meiracker AH, de Smet AA, Blankestijn PJ, van den Dorpel MA. Forearm venous distensibility predicts successful arteriovenous fistula. *Am J Kidney Dis*. 2006;47:1013–1019.
5. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation*. 2001;103:987–992.
6. Yilmaz MI, Sonmez A, Saglam M, Yaman H, Kilic S, Turker T, Unal HU, Gok M, Cetinkaya H, Eyileten T, Oguz Y, Caglar K, Vural A, Mallamaci F, Zoccali C. Longitudinal analysis of vascular function and biomarkers of metabolic bone disorders before and after renal transplantation. *Am J Nephrol*. 2013;37:126–134.
7. Recio-Mayoral A, Banerjee D, Streather C, Kaski JC. Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease—a cross-sectional study of predialysis, dialysis and kidney-transplantation patients. *Atherosclerosis*. 2011;216:446–451.
8. Demir M, Kucuk A, Sezer MT, Altuntas A, Kaya S. Malnutrition-inflammation score and endothelial dysfunction in hemodialysis patients. *J Ren Nutr*. 2010;20:377–383.
9. Morimoto S, Yurugi T, Aota Y, Sakuma T, Jo F, Nishikawa M, Iwasaka T, Maki K. Prognostic significance of ankle-brachial index, brachial-ankle pulse wave velocity, flow-mediated dilation, and nitroglycerin-mediated dilation in end-stage renal disease. *Am J Nephrol*. 2009;30:55–63.
10. Verbeke FH, Agharazii M, Boutouyrie P, Pannier B, Guerin AP, London GM. Local shear stress and brachial artery functions in end-stage renal disease. *J Am Soc Nephrol*. 2007;18:621–628.
11. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int*. 2003;63:1852–1860.
12. Dember LM, Imrey PB, Beck GJ, Cheung AK, Himmelfarb J, Huber TS, Kusek JW, Roy-Chaudhury P, Vazquez MA, Alpers CE, Robbin ML, Vita JA, Greene T, Gassman JJ, Feldman HI. Objectives and design of the hemodialysis fistula maturation study. *Am J Kidney Dis*. 2014;63:104–112.
13. Atkinson G, Batterham AM. Allometric scaling of diameter change in the original flow-mediated dilation protocol. *Atherosclerosis*. 2013;226:425–427.
14. Atkinson G, Batterham AM. The percentage flow-mediated dilation index: a large-sample investigation of its appropriateness, potential for bias and causal nexus in vascular medicine. *Vasc Med*. 2013;18:354–365.
15. Atkinson G, Batterham AM, Thijssen DH, Green DJ. A new approach to improve the specificity of flow-mediated dilation for indicating endothelial function in cardiovascular research. *J Hypertens*. 2013;31:287–291.
16. Inskip H. Standardization methods. In: Gail MH, Benichou J, eds. *Encycl Epidemiol Method*. Chichester: John Wiley and Sons;1999:871–884.
17. Schnabel RB, Schulz A, Wild PS, Sinning CR, Wilde S, Eleftheriadis M, Herkenhoff S, Zeller T, Lubos E, Lackner KJ, Warnholtz A, Gori T, Blankenberg S, Munzel T. Noninvasive vascular function measurement in the community: cross-sectional relations and comparison of methods. *Circ Cardiovasc Imaging*. 2011;4:371–380.
18. Kiani S, Aasen JG, Holbrook M, Khemka A, Sharmeen F, LeLeiko RM, Tabit CE, Farber A, Eberhardt RT, Gokce N, Vita JA, Hamburg NM. Peripheral artery disease is associated with severe impairment of vascular function. *Vasc Med*. 2013;18:72–78.
19. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, Tabak AG, McEniery CM, Wilkinson IB, Marmot MG, Singh-Manoux A, Kivimaki M. Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. *Hypertension*. 2015;66:294–300.
20. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511.
21. Benjamin EJ, Larson MG, Keyes MJ, Mitchell GF, Vasan RS, Keaney JF Jr, Lehman BT, Fan S, Osypiuk E, Vita JA. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. *Circulation*. 2004;109:613–619.
22. Herrington DM, Fan L, Drum M, Riley WA, Pusser BE, Crouse JR, Burke GL, McBurnie MA, Morgan TM, Espeland MA. Brachial flow-mediated vasodilator responses in population-based research: methods, reproducibility and effects of age, gender and baseline diameter. *J Cardiovasc Risk*. 2001;8:319–328.
23. Gokce N, Holbrook M, Duffy SJ, Demissie S, Cupples LA, Biegelsen E, Keaney JF Jr, Loscalzo J, Vita JA. Effects of race and hypertension on flow-mediated and nitroglycerin-mediated dilation of the brachial artery. *Hypertension*. 2001;38:1349–1354.
24. McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGrath LT, Henry WR, Andrews JW, Hayes JR. Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1992;35:771–776.
25. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol*. 1996;27:567–574.
26. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*. 2000;87:E10–E17.
27. Floege J, Ketteler M. Vascular calcification in patients with end-stage renal disease. *Nephrol Dial Transplant*. 2004;19(suppl 5):V59–V66.
28. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*. 2004;43:1239–1245.
29. Strain WD, Chaturvedi N, Dockery F, Shiff R, Shore AC, Bulpitt CJ, Rajkumar C. Increased arterial stiffness in Europeans and African Caribbeans with type 2 diabetes cannot be accounted for by conventional cardiovascular risk factors. *Am J Hypertens*. 2006;19:889–896.
30. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. *Hypertension*. 2005;45:592–596.
31. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol (1985)*. 2008;105:1652–1660.
32. Chan MR, Young HN, Becker YT, Yevzlin AS. Obesity as a predictor of vascular access outcomes: analysis of the USRDS DMMS Wave II study. *Semin Dial*. 2008;21:274–279.
33. Kats M, Hawxby AM, Barker J, Allon M. Impact of obesity on arteriovenous fistula outcomes in dialysis patients. *Kidney Int*. 2007;71:39–43.

# SUPPLEMENTAL MATERIAL

**Data S1**

**Statistical Appendix**

To accommodate empty cells and further stabilize directly clinical center adjusted vascular function measures, means for strata with two or fewer patients at a particular site were imputed from a fixed effects factorial linear model for age, sex, race, and diabetes with clinical sites treated as additive blocks. Full factorial age×sex×race×diabetes models were used when possible, with high order interactions deleted to obtain a reduced saturated model if necessary. Predicted means and their standard errors were imputed to these strata and thereby incorporated into the clinical site-adjusted means and standard errors. Age×sex×diabetes values also were adjusted for race, weighted to the study-wide proportion of blacks among HFM patients.

In fitting the linear mixed models, alternative covariance structures were fit by restricted maximum likelihood using a saturated fixed effects model, and allowing variance to depend on clinical site or combinations of clinical site with age, sex, race, or diabetes. The best fitting of such models was selected using the Bayesian information (BIC) criterion[34] In modeling the mean, age trends were allowed to vary nonlinearly through two degree of freedom (df) restricted cubic splines, with knots at the $5^{th}$, $20^{th}$, $80^{th}$, and $95^{th}$ age percentiles. Successive effect classes and corresponding $\alpha$'s required for statistical significance in the model reduction sequence were as follows: all four- and three-way interactions (0.5%), nonlinear age interactions (0.5%), all other pairwise interactions (2%), and nonlinear age trend (2%). Statistical significance of continuous factors was assessed by test of the slope in the reduced model or, when significant nonlinearity was found, and by the omnibus 3 df test of the overall effect.

**Supplemental Tables**

**Table S1. Baseline characteristics of the Hemodialysis Fistula Maturation Study cohort and subgroups with vascular function tests***

| | | Subcohorts with Vascular Function Tests | | | |
|---|---|---|---|---|---|
| Characteristic | Full Cohort (N=602) | FMD (N=549) | NMD (N=460) | PWV (N=448) | VOP (N=569) |
| Male | 423 (70.3%) | 388 (70.7%) | 332 (72.2%) | 316 (70.5%) | 399 (70.1%) |
| Age at vascular function assessment, years | 55.1 ± 13.4 | 55.3 ± 13.4 | 55.6 ± 13.3 | 53.9 ± 13.6 | 54.9 ± 13.4 |
| Race (self-reported) | | | | | |
| Native American, Aboriginal Canadian or Alaskan Native, First Nation, Aboriginal Australian | 13 (2.2%) | 13 (2.4%) | 11 (2.4%) | 11 (2.5%) | 13 (2.3%) |
| Asian | 13 (2.2%) | 13 (2.4%) | 12 (2.6%) | 12 (2.7%) | 12 (2.1%) |
| Native Hawaiian or Other Pacific Islander | 12 (2.0%) | 12 (2.2%) | 7 (1.5%) | 10 (2.2%) | 12 (2.1%) |
| Black, African-American, African | 264 (43.9%) | 241 (43.9%) | 203 (44.1%) | 198 (44.2%) | 244 (42.9%) |
| White/Caucasian | 283 (47.0%) | 254 (46.3%) | 215 (46.7%) | 204 (45.5%) | 271 (47.6%) |
| Multiracial | 9 (1.5%) | 9 (1.6%) | 7 (1.5%) | 7 (1.6%) | 9 (1.6%) |
| Unknown or Not Reported | 8 (1.3%) | 7 (1.3%) | 5 (1.1%) | 6 (1.3%) | 8 (1.4%) |
| Hispanic or Latino ethnicity (self-reported) | 79 (13.1%) | 75 (13.7%) | 69 (15.0%) | 64 (14.3%) | 77 (13.5%) |
| Highest education: | | | | | |
| Without high school diploma | 161 (26.7%) | 151 (27.5%) | 130 (28.3%) | 125 (27.9%) | 152 (26.7%) |
| High school graduate | 163 (27.1%) | 148 (27.0%) | 122 (26.5%) | 129 (28.8%) | 156 (27.4%) |
| Vocational, technical, or business degree | 34 (5.6%) | 32 (5.8%) | 29 (6.3%) | 22 (4.9%) | 33 (5.8%) |
| Some college, without degree | 121 (20.1%) | 110 (20.0%) | 92 (20.0%) | 90 (20.1%) | 112 (19.7%) |
| Associate's Degree | 29 (4.8%) | 27 (4.9%) | 19 (4.1%) | 24 (5.4%) | 28 (4.9%) |
| Bachelor's Degree | 48 (8.0%) | 40 (7.3%) | 35 (7.6%) | 31 (6.9%) | 45 (7.9%) |
| Master's/Doctoral/Professional school | 28 (4.7%) | 27 (4.9%) | 21 (4.6%) | 21 (4.7%) | 25 (4.4%) |
| Unknown | 18 (3.0%) | 14 (2.6%) | 12 (2.6%) | 6 (1.3%) | 18 (3.2%) |
| Not employed: | | | | | |
| Homemaker or student | 13 (2.2%) | 13 (2.4%) | 10 (2.2%) | 11 (2.5%) | 12 (2.1%) |
| Retired | 127 (21.1%) | 115 (20.9%) | 99 (21.5%) | 91 (20.3%) | 117 (20.6%) |
| Disabled | 340 (56.5%) | 317 (57.7%) | 269 (58.5%) | 259 (57.8%) | 320 (56.2%) |
| Not disabled | 44 (7.3%) | 39 (7.1%) | 29 (6.3%) | 34 (7.6%) | 44 (7.7%) |

**Table S1. Baseline characteristics of the Hemodialysis Fistula Maturation Study cohort and subgroups with vascular function tests[*]**

| | | Subcohorts with Vascular Function Tests | | | |
|---|---|---|---|---|---|
| Characteristic | Full Cohort (N=602) | FMD (N=549) | NMD (N=460) | PWV (N=448) | VOP (N=569) |
| Employed: | | | | | |
| Part-time | 31 (5.1%) | 28 (5.1%) | 23 (5.0%) | 22 (4.9%) | 30 (5.3%) |
| Full-time | 44 (7.3%) | 35 (6.4%) | 29 (6.3%) | 31 (6.9%) | 44 (7.7%) |
| Unknown | 3 (0.5%) | 2 (0.4%) | 1 (0.2%) | 0 | 2 (0.4%) |
| On maintenance dialysis at vascular function testing | 377 (62.8%) | 351 (64.2%) | 292 (63.8%) | 283 (63.3%) | 355 (62.5%) |
| BMI, $kg/m^2$ | 30.4 ± 7.56 | 30.3 ± 7.57 | 30.1 ± 7.36 | 29.2 ± 6.75 | 30.4 ± 7.59 |
| Diabetes | 353 (58.6%) | 321 (58.5%) | 269 (58.5%) | 249 (55.6%) | 330 (58.0%) |
| Vascular disease[†] | 315 (52.3%) | 285 (51.9%) | 235 (51.1%) | 226 (50.0%) | 290 (51.0%) |
| Coronary artery disease[‡] | 156 (25.9%) | 139 (25.3%) | 117 (25.4%) | 110 (24.6%) | 140 (24.6%) |
| Congestive heart failure | 165 (27.4%) | 149 (27.1%) | 126 (27.4%) | 116 (25.9%) | 152 (26.7%) |
| Cardiac arrhythmias or conduction problems | 85 (14.1%) | 81 (14.8%) | 61 (13.3%) | 53 (11.8%) | 78 (13.7%) |
| Cerebrovascular disease[‖] | 88 (14.6%) | 76 (13.8%) | 64 (13.9%) | 65 (14.5%) | 82 (14.4%) |
| Peripheral artery disease[¶] | 91 (15.1%) | 81 (14.8%) | 74 (16.1%) | 57 (12.7%) | 87 (15.3%) |
| Systolic blood pressure at vascular function testing, mm Hg | 151 ± 23.4 | 151 ± 23.5 | 153 ± 22.7 | 151 ± 23.1 | 151 ± 23.4 |
| Diastolic blood pressure at vascular function testing, mm Hg | 84.8 ± 14.3 | 84.9 ± 14.3 | 85.3 ± 14.2 | 84.8 ± 14.3 | 84.8 ± 14.3 |
| Smoking within last 12 months | 148 (24.8%) | 135 (24.8%) | 114 (25.0%) | 117 (26.2%) | 140 (24.8%) |
| Smoked within 6 hours prior to FMD determination | 44 (7.3%) | 41 (7.5%) | 37 (8.0%) | 34 (7.6%) | 42 (7.4%) |
| Serum albumin (g/dL) | 3.61 ± 0.62 | 3.62 ± 0.62 | 3.62 ± 0.62 | 3.63 ± 0.64 | 3.61 ± 0.62 |
| Serum calcium (mg/dL) | 8.89 ± 0.86 | 8.87 ± 0.84 | 8.87 ± 0.89 | 8.90 ± 0.87 | 8.89 ± 0.86 |
| Serum phosphorus (mg/dL) | 5.04 ± 1.49 | 5.04 ± 1.50 | 5.04 ± 1.50 | 5.07 ± 1.50 | 5.04 ± 1.49 |
| Brachial artery dilation | | | | | |
| Resting velocity (cm/s) | -- | 12.8 ± 5.81 | -- | -- | -- |
| Hyperemic velocity (cm/s) | -- | 82.8 ± 33.4 | -- | -- | -- |
| Baseline diameter (mm) | -- | 4.55 ± 0.81 | -- | -- | -- |
| FMD% | -- | 4.79 ± 4.96 | -- | -- | -- |
| Absolute FMD (mm) | | 0.20 ± 0.20 | | | |
| Hyperemic velocity-adjusted FMD (%/cm/s) | -- | 0.07 ± 0.11 | -- | -- | -- |
| NMD% | -- | -- | 7.22 ± 6.27 | -- | -- |
| Arterial pulse-wave velocity | | | | | |

**Table S1. Baseline characteristics of the Hemodialysis Fistula Maturation Study cohort and subgroups with vascular function tests**[*]

| | | Subcohorts with Vascular Function Tests | | | |
|---|---|---|---|---|---|
| Characteristic | Full Cohort (N=602) | FMD (N=549) | NMD (N=460) | PWV (N=448) | VOP (N=569) |
| Carotid-femoral PWV (m/s) | -- | -- | -- | 10.7 ± 3.20 | -- |
| Carotid-radial PWV (m/s) | -- | -- | -- | 8.81 ± 1.71 | -- |
| Central pulse pressure (mm Hg) | -- | -- | -- | 53.3 ± 19.1 | -- |
| Central systolic BP (mmHg) | -- | -- | -- | 137.9 ± 23.0 | -- |
| Central diastolic BP (mmHg) | -- | -- | -- | 84.6 ± 14.9 | -- |
| Augmentation index (%) | -- | -- | -- | 26.1 ± 13.1 | -- |
| Venous occlusion plethysmography | | | | | |
| Capacitance slope Δ(ml/100ml)/10mmHg | -- | -- | -- | -- | 0.53 ± 0.36 |
| Maximum venous outflow slope Δ(ml/100 ml/min)/10mmHg | -- | -- | -- | -- | 3.92 ± 2.91 |
| Mean capacitance (ml/100ml) | | | | | 1.8 ± 1.2 |
| Mean maximum venous outflow (ml/100 ml/min) | | | | | 16.7 ± 13.0 |
| Forearm volume ($mm^3$) | | | | | 62.7 ± 16.8 |

[*]Percentage or mean ± SD

[†]History of any of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty, congestive heart failure, cardiac arrhythmias or conduction problems, stroke, transient ischemic attack, carotid endarterectomy, carotid artery angioplasty, lower extremity arterial bypass surgery or angioplasty, non-traumatic amputation, and claudication

[‡]Angina, coronary artery angioplasty or bypass surgery, or myocardial infarction

[‖]Stroke, transient ischemic attack, carotid endarterectomy, or carotid angioplasty

[¶]Claudication, lower extremity angioplasty or bypass surgery, or non-traumatic amputation

Abbreviations: FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation; PWV, pulse wave velocity; VOP, venous occlusion plethysmography

**Table S2. Additional vascular function measures, by age, sex, race, and diabetes status, directly-adjusted for clinical center[*]**

| | Age | | | | | Sex | | Black Race | | Diabetes | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤ 40 | 40-49 | 50-59 | 60-69 | ≥ 70 | Female | Male | Yes | No | Yes | No |
| **Measure** | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) |
| **Brachial Artery Dilation** | | | | | | | | | | | |
| Resting velocity (cm/s) | 14.14 (2.70) | 13.38 (2.18) | 13.14 (1.76) | 11.99 (1.61) | 12.80 (1.71) | 13.58 (1.76) | 12.74 (2.14) | 12.49 (2.05) | 13.52 (2.07) | 13.44 (1.84) | 12.40 (2.31) |
| Baseline diameter (mm) | 4.36 (0.28) | 4.30 (0.26) | 4.47 (0.30) | 4.84 (0.35) | 4.69 (0.25) | 3.96 (0.23) | 4.76 (0.30) | 4.61 (0.34) | 4.41 (0.31) | 4.56 (0.32) | 4.52 (0.32) |
| Absolute FMD (mm) | 0.24 (0.09) | 0.20 (0.06) | 0.19 (0.07) | 0.18 (0.08) | 0.15 (0.05) | 0.21 (0.07) | 0.19 (0.07) | 0.17 (0.07) | 0.21 (0.07) | 0.16 (0.06) | 0.24 (0.08) |
| Hyperemic velocity-adjusted FMD% (%/cm/s) | 0.07 (0.03) | 0.06 (0.02) | 0.08 (0.07) | 0.07 (0.04) | 0.05 (0.02) | 0.12 (0.09) | 0.06 (0.03) | 0.08 (0.06) | 0.06 (0.03) | 0.05 (0.03) | 0.09 (0.07) |
| **Arterial Pulse-Wave Velocity** | | | | | | | | | | | |
| Central systolic bp (mmHg) | 130.6 (7.7) | 133.7 (8.3) | 138.2 (7.5) | 136.1 (9.7) | 137.1 (8.0) | 138.8 (9.7) | 135.1 (8.2) | 134.3 (8.6) | 135.5 (7.7) | 139.9 (9.3) | 131.1 (6.9) |
| Central diastolic bp (mmHg) | 93.2 (5.3) | 87.4 (5.7) | 85.4 (4.9) | 77.7 (4.6) | 74.5 (4.6) | 82.8 (5.9) | 84.9 (5.6) | 85.7 (5.1) | 81.3 (5.1) | 82.0 (5.6) | 86.3 (5.3) |
| Central pulse pressure (mmHg) | 37.5 (3.6) | 46.2 (5.8) | 52.7 (6.3) | 58.4 (7.2) | 62.7 (7.3) | 56.1 (7.1) | 50.2 (6.7) | 48.7 (6.9) | 54.2 (6.2) | 58.0 (7.6) | 44.8 (5.5) |
| Augmentation index (%) | 18.20 (4.90) | 21.03 (5.08) | 28.49 (3.87) | 27.98 (5.27) | 30.58 (3.41) | 31.49 (4.32) | 23.50 (5.07) | 22.29 (6.42) | 26.71 (4.45) | 25.36 (5.36) | 25.58 (4.96) |
| **Venous Occlusion Plethysmography** | | | | | | | | | | | |
| Mean capacitance (ml/100ml) | 2.07 (0.54) | 1.67 (0.31) | 1.65 (0.33) | 1.69 (0.46) | 1.53 (0.29) | 1.66 (0.36) | 1.73 (0.40) | 1.67 (0.37) | 1.73 (0.39) | 1.55 (0.32) | 1.90 (0.46) |
| Mean maximum venous outflow (ml/100 ml/min) | 18.64 (5.20) | 15.11 (3.53) | 14.68 (3.87) | 15.19 (4.11) | 14.19 (2.70) | 14.38 (4.07) | 15.77 (3.92) | 15.05 (3.91) | 15.19 (3.99) | 13.89 (3.48) | 17.26 (4.51) |
| Forearm volume ($mm^3$) | 63.51 (5.97) | 65.16 (6.74) | 62.33 (6.35) | 64.90 (6.37) | 63.87 (4.43) | 53.51 (5.33) | 68.09 (6.01) | 65.93 (6.14) | 64.47 (6.16) | 64.94 (6.49) | 62.42 (6.24) |

[*]Values for age × sex ×diabetes × clinical center combinations with 2 or fewer patients were smoothed by imputation with fitted values from a fixed effects models with additive clinical center effects and a saturated model for the other variables, minimally reduced if necessary to achieve an identifiable model. Prior to such modeling, cells for each combination were initially adjusted for the variable omitted from that combination (i.e., race for the age × sex × diabetes combinations), by weighting the levels of the omitted variable uniformly by their proportions in the full HFM Study sample.

Abbreviations: FMD, flow-mediated dilation; bp, blood pressure

**Table S3. Vascular function measures for age × sex x black race combinations, directly adjusted for clinical center.***

| | | | Age, years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| **Measure** | **Male** | **Black** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** |
| Brachial artery resting velocity (cm/sec) | N | N | 18.81 | 0.77 | 12.52 | 0.6 | 13.86 | 0.52 | 13.18 | 0.49 | 14.15 | 1.01 |
| | N | Y | 13.38 | 0.7 | 11.46 | 0.63 | 12.34 | 0.42 | 12.32 | 0.49 | 8.49 | 1.13 |
| | Y | N | 12.42 | 0.59 | 14.72 | 0.45 | 13.27 | 0.55 | 11.11 | 0.42 | 13.63 | 0.54 |
| | Y | Y | 13.73 | 0.56 | 12.51 | 0.61 | 12.01 | 0.48 | 11.26 | 0.35 | 9.32 | 0.69 |
| Hyperemic velocity (cm/sec) | N | N | 124.25 | 4.22 | 89.86 | 3.47 | 85.59 | 2.99 | 78.16 | 2.69 | 82.1 | 3.38 |
| | N | Y | 101.45 | 5.26 | 108.21 | 3.33 | 76.75 | 2.89 | 56.57 | 3.05 | 45.7 | 5.49 |
| | Y | N | 103.45 | 3.36 | 99.02 | 2.87 | 87.13 | 3.12 | 76.28 | 3.22 | 69.54 | 2.9 |
| | Y | Y | 88.61 | 3 | 81.13 | 3.56 | 75.56 | 2.94 | 74.01 | 2.88 | 57.81 | 3.41 |
| Brachial artery resting diameter (mm) | N | N | 3.45 | 0.09 | 3.9 | 0.08 | 4.04 | 0.07 | 3.93 | 0.06 | 4.01 | 0.08 |
| | N | Y | 4.11 | 0.09 | 3.98 | 0.08 | 4.04 | 0.06 | 4.06 | 0.07 | 4.93 | 0.13 |
| | Y | N | 4.59 | 0.07 | 4.22 | 0.06 | 4.64 | 0.07 | 5 | 0.08 | 4.85 | 0.07 |
| | Y | Y | 4.53 | 0.07 | 4.69 | 0.07 | 4.9 | 0.1 | 5.07 | 0.1 | 5.51 | 0.1 |
| Brachial artery FMD% | N | N | 7.85 | 0.55 | 4.72 | 0.48 | 5.83 | 0.51 | 4.11 | 0.42 | 3.23 | 0.62 |
| | N | Y | 3.91 | 0.71 | 5.43 | 0.52 | 5.09 | 0.37 | 4.62 | 0.41 | -0.48 | 0.93 |
| | Y | N | 5.95 | 0.45 | 5.83 | 0.46 | 4.55 | 0.53 | 3.96 | 0.45 | 2.54 | 0.44 |
| | Y | Y | 4.18 | 0.48 | 4.24 | 0.47 | 2.6 | 0.44 | 4.68 | 0.47 | 3.77 | 0.62 |
| Absolute FMD (mm) | N | N | 0.26 | 0.02 | 0.17 | 0.02 | 0.22 | 0.02 | 0.15 | 0.02 | 0.12 | 0.02 |
| | N | Y | 0.14 | 0.03 | 0.2 | 0.02 | 0.2 | 0.01 | 0.18 | 0.02 | -0.03 | 0.04 |
| | Y | N | 0.26 | 0.02 | 0.23 | 0.02 | 0.2 | 0.02 | 0.19 | 0.02 | 0.12 | 0.02 |
| | Y | Y | 0.18 | 0.02 | 0.19 | 0.02 | 0.11 | 0.02 | 0.21 | 0.02 | 0.17 | 0.03 |
| Hyperemic velocity-adjusted FMD% | N | N | 0.07 | 0.01 | 0.09 | 0.01 | 0.09 | 0.01 | 0.06 | 0.01 | 0.05 | 0.01 |
| | N | Y | 0.04 | 0.02 | 0.07 | 0.01 | 0.09 | 0.02 | 0.08 | 0.01 | 0.01 | 0.01 |
| | Y | N | 0.08 | 0.01 | 0.08 | 0.01 | 0.07 | 0.01 | 0.07 | 0.01 | 0.04 | 0.01 |
| | Y | Y | 0.06 | 0.01 | 0.06 | 0.01 | 0.04 | 0.01 | 0.08 | 0.01 | 0.07 | 0.01 |
| Brachial artery NMD% | N | N | 11.83 | 0.88 | 11.7 | 0.71 | 10.78 | 0.87 | 6.65 | 0.58 | 6.69 | 0.69 |
| | N | Y | 9.41 | 1.06 | 15.56 | 0.75 | 8.75 | 0.61 | 7.34 | 0.56 | 7.71 | 1.21 |
| | Y | N | 8.85 | 0.85 | 9.08 | 0.67 | 7.14 | 0.53 | 5.97 | 0.49 | 3.95 | 0.44 |
| | Y | Y | 7.11 | 0.52 | 7.41 | 0.6 | 5.17 | 0.78 | 6.79 | 0.59 | 3.22 | 0.8 |
| Carotid-Femoral PWV (m/sec) | N | N | 9.4 | 0.3 | 9.55 | 0.3 | 9.52 | 0.36 | 10.32 | 0.29 | 11.97 | 0.36 |

**Table S3. Vascular function measures for age × sex x black race combinations, directly adjusted for clinical center.[*]**

| | | | Age, years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| **Measure** | **Male** | **Black** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** |
| | N | Y | 8.84 | 0.34 | 8.28 | 0.33 | 11.76 | 0.31 | 11 | 0.29 | 13.99 | 0.62 |
| | Y | N | 8.84 | 0.27 | 9.98 | 0.24 | 10.57 | 0.21 | 12.16 | 0.36 | 12.62 | 0.29 |
| | Y | Y | 8.64 | 0.25 | 9.41 | 0.21 | 10.58 | 0.24 | 10.49 | 0.23 | 9.96 | 0.43 |
| Carotid-Radial PWV (m/sec) | N | N | 9.7 | 0.2 | 8.11 | 0.21 | 8.06 | 0.17 | 8.09 | 0.18 | 8.26 | 0.23 |
| | N | Y | 8.6 | 0.22 | 8.93 | 0.21 | 8.88 | 0.14 | 9.31 | 0.18 | 10.63 | 0.37 |
| | Y | N | 9.34 | 0.16 | 8.77 | 0.15 | 8.72 | 0.17 | 9.14 | 0.22 | 9.04 | 0.21 |
| | Y | Y | 9.29 | 0.16 | 9.92 | 0.14 | 9.3 | 0.15 | 9.14 | 0.14 | 8.53 | 0.26 |
| Central pulse Pressure (mmHg) | N | N | 53.72 | 2.03 | 62.47 | 2.22 | 53.66 | 1.82 | 69.18 | 2.06 | 70.78 | 2.37 |
| | N | Y | 47.31 | 2.26 | 46.64 | 2.06 | 58.44 | 1.51 | 64.07 | 1.8 | 83.73 | 3.76 |
| | Y | N | 37.91 | 1.44 | 51.51 | 1.7 | 55.93 | 1.59 | 56.52 | 2.23 | 62.4 | 2.28 |
| | Y | Y | 38.66 | 1.45 | 41.61 | 1.38 | 47.46 | 1.67 | 54.66 | 1.49 | 52.58 | 2.58 |
| Central systolic BP (mmHg) | N | N | 158.84 | 2.78 | 136.5 | 2.71 | 133.92 | 2.79 | 144.14 | 2.54 | 148.49 | 3.02 |
| | N | Y | 147.29 | 3.11 | 141.05 | 2.82 | 141.12 | 1.9 | 150.21 | 2.6 | 162.85 | 4.99 |
| | Y | N | 135.35 | 2.13 | 135.95 | 2.27 | 139.9 | 1.79 | 134.45 | 3.2 | 133.23 | 2.39 |
| | Y | Y | 133.55 | 2.09 | 134.4 | 2.15 | 137.14 | 2.09 | 137.82 | 1.97 | 132.02 | 3.39 |
| Central diastolic BP (mmHg) | N | N | 104.59 | 1.7 | 75.38 | 1.53 | 79.71 | 1.46 | 74.39 | 1.29 | 77.45 | 1.76 |
| | N | Y | 99.69 | 1.91 | 95.27 | 1.66 | 83.53 | 1.15 | 85.37 | 1.6 | 77.6 | 2.92 |
| | Y | N | 97.43 | 1.35 | 84.06 | 1.21 | 83.85 | 1.57 | 77.76 | 1.42 | 71.71 | 1.67 |
| | Y | Y | 94.97 | 1.32 | 92.91 | 1.30 | 89.64 | 1.49 | 82.69 | 1.19 | 78.55 | 2.06 |
| Augmentation Index (%) | N | N | 35.8 | 1.61 | 32.15 | 1.41 | 30.02 | 1.33 | 34.83 | 1.38 | 36.89 | 1.66 |
| | N | Y | 21.84 | 1.72 | 29.26 | 1.61 | 31.65 | 1.06 | 31.76 | 1.55 | 30.92 | 2.69 |
| | Y | N | 17.2 | 1.50 | 21.41 | 1.13 | 27.62 | 1.13 | 28.84 | 1.45 | 27.95 | 1.31 |
| | Y | Y | 14.68 | 1.23 | 18.24 | 1.35 | 24.25 | 1.22 | 26.7 | 1.31 | 21.83 | 1.90 |
| Capacitance slope Δ(ml/100 ml)/10mmHg) | N | N | 0.57 | 0.04 | 0.43 | 0.02 | 0.44 | 0.03 | 0.46 | 0.03 | 0.45 | 0.05 |
| | N | Y | 0.46 | 0.03 | 0.31 | 0.03 | 0.53 | 0.02 | 0.59 | 0.02 | 0.37 | 0.06 |
| | Y | N | 0.59 | 0.03 | 0.54 | 0.03 | 0.54 | 0.03 | 0.54 | 0.05 | 0.54 | 0.03 |
| | Y | Y | 0.52 | 0.04 | 0.45 | 0.02 | 0.47 | 0.02 | 0.53 | 0.02 | 0.40 | 0.03 |
| Capacitance mean (ml/100ml) | N | N | 2.01 | 0.2 | 1.33 | 0.08 | 1.45 | 0.08 | 1.42 | 0.07 | 1.20 | 0.16 |
| | N | Y | 1.68 | 0.09 | 1.28 | 0.12 | 1.84 | 0.06 | 1.73 | 0.07 | 0.96 | 0.20 |
| | Y | N | 2.20 | 0.07 | 1.88 | 0.09 | 1.69 | 0.07 | 1.84 | 0.17 | 1.63 | 0.09 |
| | Y | Y | 1.69 | 0.10 | 1.54 | 0.07 | 1.57 | 0.07 | 1.74 | 0.09 | 1.10 | 0.10 |

**Table S3. Vascular function measures for age × sex x black race combinations, directly adjusted for clinical center.[*]**

| | | | Age, years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| **Measure** | **Male** | **Black** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** | **Mean** | **SE** |
| Maximum venous outflow slope (Δ(ml/100 ml/min)/10mmHg) | N | N | 3.71 | 0.36 | 2.64 | 0.22 | 3.08 | 0.22 | 3.58 | 0.26 | 2.91 | 0.38 |
| | N | Y | 3.44 | 0.27 | 2.38 | 0.24 | 3.56 | 0.19 | 3.96 | 0.23 | 1.67 | 0.50 |
| | Y | N | 5.08 | 0.27 | 3.99 | 0.24 | 4.04 | 0.33 | 3.59 | 0.30 | 3.41 | 0.22 |
| | Y | Y | 3.73 | 0.22 | 3.50 | 0.16 | 3.33 | 0.14 | 3.93 | 0.29 | 2.44 | 0.28 |
| Mean maximum venous outflow (ml/100 ml/min) | N | N | 17.43 | 2.26 | 10.41 | 0.98 | 12.29 | 1.07 | 13.2 | 0.75 | 12.91 | 1.75 |
| | N | Y | 14.54 | 1.03 | 10.68 | 1.14 | 15.19 | 0.78 | 15.58 | 0.76 | 6.81 | 2.21 |
| | Y | N | 21.75 | 0.75 | 16.79 | 0.89 | 16.43 | 0.99 | 15.01 | 1.30 | 15.68 | 0.79 |
| | Y | Y | 14.64 | 0.86 | 15.19 | 1.37 | 12.95 | 0.77 | 17.74 | 1.14 | 10.26 | 1.16 |
| Forearm Volume ($mm^3$) | N | N | 48.2 | 1.97 | 50.82 | 1.46 | 55.62 | 1.67 | 53.31 | 1.57 | 49.64 | 1.55 |
| | N | Y | 47.26 | 1.95 | 68.07 | 1.94 | 53.79 | 1.11 | 55.82 | 1.67 | 60.36 | 2.79 |
| | Y | N | 63.05 | 1.48 | 63.84 | 1.59 | 62.71 | 1.64 | 69.69 | 1.92 | 65.28 | 1.16 |
| | Y | Y | 73.9 | 1.47 | 74.04 | 2.38 | 71.04 | 1.52 | 67.10 | 1.42 | 75.34 | 1.92 |

[*]Values for age × sex × race × clinical center combinations with 2 or fewer patients were smoothed by imputation with fitted values from a fixed effects models with additive clinical center effects and a saturated model for the other variables, minimally reduced if necessary to achieve an identifiable model. Prior to such modeling, cells for each combination were initially adjusted for the variable omitted from that combination (i.e., Diabetes for the Age × Sex × Race and Race for the Age × Sex × Diabetes combinations), by weighting the levels of the omitted variable uniformly by their proportions in the full HFM Study sample.

Abbreviations: FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation; PWV, pulse wave velocity; BP, blood pressure; CAP, capacitance; MVO, maximum venous outflow; N, no; Y, yes

**Table S4: Vascular function measures for age × sex × diabetes combinations, directly adjusted for clinical center[*].**

| | | | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| Measure | Male | Diabetes | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Brachial artery resting velocity (cm/sec) | N | N | 16.15 | 0.76 | 11.51 | 0.71 | 11.88 | 0.46 | 12.85 | 0.57 | 8.61 | 1.37 |
| | N | Y | 16.58 | 0.72 | 12.43 | 0.56 | 14.09 | 0.49 | 12.75 | 0.44 | 13.76 | 0.85 |
| | Y | N | 14.51 | 0.75 | 10.94 | 0.34 | 12.44 | 0.67 | 12.44 | 0.67 | 10.87 | 0.82 |
| | Y | Y | 11.94 | 0.47 | 15.71 | 0.59 | 12.9 | 0.43 | 11.39 | 0.41 | 12.31 | 0.46 |
| Brachial artery hyperemic velocity (cm/sec) | N | N | 107.47 | 3.47 | 106.06 | 4.04 | 89.97 | 2.93 | 78.1 | 3.28 | 46.83 | 6.33 |
| | N | Y | 118.78 | 5.08 | 92.36 | 3.01 | 75.83 | 2.92 | 61.86 | 2.55 | 79.32 | 2.78 |
| | Y | N | 105.87 | 3.06 | 89.17 | 2.56 | 88.64 | 3.44 | 88.64 | 3.44 | 66.27 | 3.91 |
| | Y | Y | 90.53 | 3.27 | 92.4 | 3.38 | 77.31 | 2.8 | 75.45 | 3.16 | 62.95 | 2.58 |
| Brachial artery baseline diameter (mm) | N | N | 3.67 | 0.06 | 3.66 | 0.09 | 4.01 | 0.07 | 3.77 | 0.08 | 5 | 0.15 |
| | N | Y | 3.79 | 0.1 | 4.12 | 0.07 | 4.06 | 0.06 | 4.14 | 0.06 | 4.01 | 0.07 |
| | Y | N | 4.72 | 0.06 | 4.42 | 0.06 | 4.76 | 0.09 | 4.76 | 0.09 | 5.34 | 0.09 |
| | Y | Y | 4.46 | 0.07 | 4.44 | 0.07 | 4.75 | 0.08 | 5.02 | 0.09 | 5 | 0.07 |
| Brachial artery FMD% | N | N | 9.18 | 0.55 | 7.71 | 0.58 | 7.61 | 0.45 | 5.48 | 0.41 | -1.69 | 1.17 |
| | N | Y | 3.94 | 0.65 | 3.16 | 0.44 | 4.02 | 0.46 | 3.53 | 0.42 | 3.88 | 0.41 |
| | Y | N | 6.13 | 0.48 | 6.13 | 0.44 | 4.98 | 0.73 | 4.98 | 0.73 | 1.89 | 0.56 |
| | Y | Y | 4.48 | 0.45 | 4.42 | 0.46 | 2.77 | 0.31 | 3.45 | 0.41 | 3.93 | 0.48 |
| Brachial artery absolute FMD (mm) | N | N | 0.33 | 0.02 | 0.27 | 0.02 | 0.3 | 0.02 | 0.21 | 0.02 | -0.07 | 0.05 |
| | N | Y | 0.12 | 0.03 | 0.12 | 0.02 | 0.15 | 0.02 | 0.14 | 0.02 | 0.14 | 0.02 |

**Table S4: Vascular function measures for age × sex × diabetes combinations, directly adjusted for clinical center[*].**

| | | | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| Measure | Male | Diabetes | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| | Y | N | 0.27 | 0.02 | 0.25 | 0.02 | 0.22 | 0.03 | 0.22 | 0.03 | 0.09 | 0.02 |
| | Y | Y | 0.19 | 0.02 | 0.18 | 0.02 | 0.12 | 0.01 | 0.16 | 0.02 | 0.18 | 0.02 |
| Brachial artery hyperemic velocity-adjusted FMD% | N | N | 0.09 | 0.01 | 0.12 | 0.01 | 0.14 | 0.02 | 0.08 | 0.01 | -0.02 | 0.02 |
| | N | Y | 0.03 | 0.02 | 0.05 | 0.01 | 0.06 | 0.01 | 0.06 | 0.01 | 0.06 | 0.01 |
| | Y | N | 0.08 | 0.01 | 0.08 | 0.01 | 0.07 | 0.01 | 0.07 | 0.01 | 0.03 | 0.01 |
| | Y | Y | 0.06 | 0.01 | 0.06 | 0.01 | 0.05 | 0.01 | 0.05 | 0.01 | 0.07 | 0.01 |
| Brachial artery NMD% | N | N | 13.28 | 0.76 | 18.23 | 0.81 | 11.83 | 0.57 | 7.86 | 0.62 | 7.64 | 1.34 |
| | N | Y | 8.98 | 1.03 | 10.04 | 0.68 | 8.51 | 0.85 | 6.32 | 0.54 | 6.8 | 0.62 |
| | Y | N | 9.36 | 0.61 | 10.43 | 0.68 | 8.22 | 0.76 | 8.22 | 0.76 | 2.46 | 0.72 |
| | Y | Y | 7.18 | 0.78 | 6.87 | 0.62 | 4.9 | 0.56 | 5.56 | 0.5 | 4.44 | 0.53 |
| Carotid-Femoral PWV (m/sec) | N | N | 7.28 | 0.23 | 7.71 | 0.31 | 8.63 | 0.24 | 10.1 | 0.31 | 13.18 | 0.71 |
| | N | Y | 10.47 | 0.34 | 9.89 | 0.31 | 11.84 | 0.38 | 10.99 | 0.28 | 12.65 | 0.3 |
| | Y | N | 7.94 | 0.21 | 8.01 | 0.21 | 9.17 | 0.23 | 9.17 | 0.23 | 11.58 | 0.36 |
| | Y | Y | 9.32 | 0.28 | 10.93 | 0.23 | 11.56 | 0.22 | 11.3 | 0.32 | 11.34 | 0.34 |
| Carotid-Radial PWV (m/sec) | N | N | 8.9 | 0.16 | 8.01 | 0.21 | 8.47 | 0.16 | 8.29 | 0.18 | 10.56 | 0.44 |
| | N | Y | 9.43 | 0.22 | 8.79 | 0.2 | 8.39 | 0.15 | 8.87 | 0.17 | 8.45 | 0.17 |
| | Y | N | 8.49 | 0.13 | 8.62 | 0.14 | 8.92 | 0.2 | 8.92 | 0.2 | 9.1 | 0.23 |
| | Y | Y | 9.9 | 0.17 | 9.74 | 0.15 | 9.02 | 0.13 | 9.11 | 0.2 | 8.61 | 0.23 |
| Central pulse pressure (mmHg) | N | N | 35.54 | 1.46 | 46.86 | 2.06 | 50.33 | 1.5 | 67.5 | 1.82 | 79.05 | 4.4 |

**Table S4: Vascular function measures for age × sex × diabetes combinations, directly adjusted for clinical center[*].**

| | | | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| Measure | Male | Diabetes | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| | N | Y | 61.63 | 2.36 | 61.45 | 2.18 | 59.61 | 1.78 | 66.49 | 2 | 74.78 | 1.88 |
| | Y | N | 33.17 | 1.18 | 37.96 | 1.39 | 44.93 | 1.55 | 44.93 | 1.55 | 52.19 | 2.19 |
| | Y | Y | 41.8 | 1.54 | 53.54 | 1.65 | 57.24 | 1.64 | 56.28 | 1.98 | 62.15 | 2.47 |
| Central systolic bp (mmHg) | N | N | 125.27 | 2.11 | 123.07 | 2.78 | 133.67 | 2.11 | 149.62 | 2.43 | 165.93 | 5.78 |
| | N | Y | 173.67 | 3.2 | 149.37 | 2.71 | 139.54 | 2.61 | 144.88 | 2.59 | 147.11 | 2.45 |
| | Y | N | 121.05 | 1.76 | 125.96 | 2.13 | 130.25 | 2.13 | 130.25 | 2.13 | 129.41 | 3.01 |
| | Y | Y | 144.03 | 2.25 | 141.79 | 2.24 | 144.59 | 1.77 | 132.88 | 2.99 | 134.99 | 2.69 |
| Central diastolic bp (mmHg) | N | N | 89.55 | 1.46 | 76.89 | 1.63 | 83.9 | 1.37 | 81.8 | 1.48 | 85.32 | 3.43 |
| | N | Y | 111.44 | 1.91 | 89.36 | 1.54 | 79.66 | 1.31 | 77.5 | 1.36 | 72.04 | 1.36 |
| | Y | N | 88.35 | 1.16 | 87.52 | 1.33 | 85.28 | 1.5 | 85.28 | 1.5 | 76.35 | 2.08 |
| | Y | Y | 101.94 | 1.4 | 88.33 | 1.19 | 87.23 | 1.53 | 76.15 | 1.39 | 73.62 | 1.67 |
| Augmentation index (%) | N | N | 25.68 | 1.4 | 33.47 | 1.61 | 33.3 | 1.17 | 37.5 | 1.65 | 31 | 3.17 |
| | N | Y | 32.34 | 1.75 | 29.04 | 1.41 | 28.95 | 1.24 | 30.64 | 1.32 | 36.51 | 1.28 |
| | Y | N | 12.93 | 1.3 | 16.51 | 1.28 | 26.01 | 1.22 | 26.01 | 1.22 | 26.23 | 1.63 |
| | Y | Y | 18.29 | 1.43 | 22.45 | 1.18 | 26.2 | 1.12 | 25.49 | 1.49 | 24.53 | 1.51 |
| Capacitance slope (Δ(ml/100 ml)/10mmHg) | N | N | 0.55 | 0.05 | 0.42 | 0.03 | 0.54 | 0.03 | 0.58 | 0.02 | 0.26 | 0.09 |
| | N | Y | 0.5 | 0.03 | 0.34 | 0.02 | 0.43 | 0.03 | 0.47 | 0.02 | 0.53 | 0.03 |
| | Y | N | 0.62 | 0.06 | 0.51 | 0.01 | 0.51 | 0.03 | 0.51 | 0.03 | 0.45 | 0.04 |
| | Y | Y | 0.52 | 0.02 | 0.49 | 0.03 | 0.5 | 0.03 | 0.48 | 0.03 | 0.5 | 0.03 |

**Table S4: Vascular function measures for age × sex × diabetes combinations, directly adjusted for clinical center[*].**

| | | | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| Measure | Male | Diabetes | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Mean capacitance (ml/100ml) | N | N | 1.97 | 0.25 | 1.63 | 0.12 | 1.94 | 0.09 | 1.64 | 0.07 | 0.38 | 0.29 |
| | N | Y | 1.79 | 0.1 | 1.08 | 0.08 | 1.41 | 0.07 | 1.49 | 0.07 | 1.59 | 0.09 |
| | Y | N | 2.39 | 0.11 | 1.73 | 0.05 | 1.71 | 0.06 | 1.71 | 0.06 | 1.41 | 0.11 |
| | Y | Y | 1.68 | 0.07 | 1.72 | 0.1 | 1.59 | 0.07 | 1.56 | 0.1 | 1.38 | 0.08 |
| MVO slope (Δ(ml/100 ml/min)/10mmHg) | N | N | 3.65 | 0.41 | 2.68 | 0.26 | 3.93 | 0.26 | 3.82 | 0.2 | 1.01 | 0.68 |
| | N | Y | 3.54 | 0.27 | 2.42 | 0.21 | 2.84 | 0.18 | 3.7 | 0.27 | 3.3 | 0.22 |
| | Y | N | 4.8 | 0.33 | 3.97 | 0.16 | 3.65 | 0.19 | 3.65 | 0.19 | 2.78 | 0.3 |
| | Y | Y | 4.25 | 0.2 | 3.63 | 0.24 | 3.78 | 0.31 | 3.42 | 0.26 | 3.12 | 0.21 |
| Mean MVO (ml/100ml/min) | N | N | 18.97 | 2.87 | 13.38 | 1.17 | 15.86 | 1.12 | 16.16 | 0.85 | 4.4 | 3.05 |
| | N | Y | 14.16 | 1.06 | 8.54 | 0.96 | 11.98 | 0.88 | 12.92 | 0.7 | 14.27 | 0.97 |
| | Y | N | 23 | 0.88 | 16 | 0.57 | 15.37 | 0.67 | 15.37 | 0.67 | 13.32 | 1.24 |
| | Y | Y | 15.5 | 0.73 | 16.14 | 1.28 | 14.54 | 1 | 13.96 | 0.97 | 13.23 | 0.76 |
| Forearm volume (ml) | N | N | 51.16 | 1.68 | 53.85 | 1.68 | 54.88 | 1.2 | 55.87 | 1.56 | 60.31 | 3.08 |
| | N | Y | 45.36 | 2.08 | 61.73 | 1.63 | 54.77 | 1.59 | 53.37 | 1.62 | 50.12 | 1.34 |
| | Y | N | 64.43 | 1.42 | 66.83 | 1.76 | 62.74 | 1.99 | 62.74 | 1.99 | 66.2 | 1.86 |
| | Y | Y | 70.28 | 1.49 | 69.42 | 2 | 69.01 | 1.33 | 69.74 | 1.85 | 72.26 | 1.26 |

**Table S4: Vascular function measures for age × sex × diabetes combinations, directly adjusted for clinical center[*].**

| | | | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 40 | | 40-49 | | 50-59 | | 60-69 | | ≥ 70 | |
| Measure | Male | Diabetes | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |

[*]Values for age × sex ×diabetes × clinical center combinations with 2 or fewer patients were smoothed by imputation with fitted values from a fixed effects models with additive clinical center effects and a saturated model for the other variables, minimally reduced if necessary to achieve an identifiable model. Prior to such modeling, cells for each combination were initially adjusted for the variable omitted from that combination (i.e., race for the age × sex × diabetes combinations), by weighting the levels of the omitted variable uniformly by their proportions in the full HFM Study sample.

Abbreviations: FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation; PWV, pulse wave velocity; BP, blood pressure; CAP, capacitance; MVO, maximum venous outflow; N, no; Y, yes

**Table S5. Allometrically adjusted differences in flow-mediated and nitroglycerin-mediated dilation associated with pre-specified predictorsadjusted for clinical center, age, sex, black race, and diabetes, from mixed multiple linear regression models.**

| | Flow-Mediated Dilation % | | | Nitroglycerin-Mediated Dilation % | | |
|---|---|---|---|---|---|---|
| **Measure** | **Estimate** | **SE** | **p-value** | **Estimate** | **SE** | **p-value** |
| BMI (per kg/m$^2$) | 0.012 | 0.021 | 0.58 | 0.02 | 0.03 | 0.55 |
| Systolic bp (per 10 mm Hg) | -0.15 | 0.07 | 0.034 | -0.44 | 0.1x | < 0.0001 |
| Diastolic bp (per 10 mm Hg) | 0.021 | 0.12 | 0.86 | -0.08 | 0.17 | 0.63 |
| Serum albumin (per g/dL) | -0.18 | 0.27 | 0.52 | 0.33 | 0.37 | 0.37 |
| Serum calcium (per mg/dL) | 0.04 | 0.20 | 0.86 | 0.31 | 0.25 | 0.23 |
| Serum phosphorus (per mg/dL) | Nonlinear (p=0.02, p=0.009 for nonlinearity), with slightly attenuated component linear decline (-0.9 vs. -1.1) vs. FMD%. | | | -0.21 | 0.15 | 0.16 |
| History of vascular disease* | -0.70 | 0.33 | 0.04 | -1.05 | 0.47 | 0.04 |
| Cigarette use past 12 months | -0.70 | 0.38 | 0.052 | -0. 42 | 0.51 | 0.41 |
| Maintenance dialysis | 1.30 | 0.3x | 0.0001 | 0.47 | 0.47 | 0.31 |

*History of any of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty, congestive heart failure, cardiac arrhythmias or conduction problems, stroke, transient ischemic attack, carotid endarterectomy, carotid artery angioplasty, lower extremity arterial bypass surgery or angioplasty, non-traumatic amputation, and claudication

Abbreviations: BMI, body mass index; bp, blood pressure