

# Association between Preoperative Vascular Function and Postoperative Arteriovenous Fistula Development

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## ABSTRACT

Arteriovenous fistula (AVF) maturation failure is the primary cause of dialysis vascular access dysfunction. To evaluate whether preoperative vascular functional properties predict postoperative AVF measurements, patients enrolled in the Hemodialysis Fistula Maturation Study underwent up to five preoperative vascular function tests (VFTs): flow-mediated dilation (FMD), nitroglycerin-mediated dilation (NMD), carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity, and venous occlusion plethysmography. We used mixed effects multiple regression analyses to relate each preoperative VFT to ultrasound measurements of AVF blood flow rate and venous diameter at 1 day, 2 weeks, and 6 weeks after AVF placement. After controlling for AVF location, preoperative ultrasound measurements, and demographic factors (age, sex, race, and dialysis status), greater NMD associated with greater 6-week AVF blood flow rate and AVF diameter (per absolute 10% difference in NMD: change in blood flow rate = 14.0%; 95% confidence interval [95% CI], 3.7% to 25.3%;  $P < 0.01$ ; change in diameter = 0.45 mm; 95% CI, 0.25 to 0.65 mm;  $P < 0.001$ ). Greater FMD also associated with greater increases in 6-week AVF blood flow rate and AVF diameter (per absolute 10% difference in FMD: change in blood flow rate = 11.6%; 95% CI, 0.6% to 23.9%;  $P = 0.04$ ; change in diameter = 0.31 mm; 95% CI, 0.05 to 0.57 mm;  $P = 0.02$ ). None of the remaining VFT parameters exhibited consistent statistically significant relationships with both postoperative AVF blood flow rate and diameter. In conclusion, preoperative NMD and FMD positively associated with changes in 6-week AVF blood flow rate and diameter, suggesting that native functional arterial properties affect AVF development.

*J Am Soc Nephrol* 27: 3788–3795, 2016. doi: 10.1681/ASN.2015020141

Although the arteriovenous fistula (AVF) is considered the preferred type of chronic hemodialysis vascular access,<sup>1</sup> a substantial proportion of new AVFs fails to mature sufficiently to be used for dialysis.<sup>2–4</sup> AVFs are created by a direct anastomosis between a native artery and vein, and successful AVF maturation requires substantial increase in the blood flow rate and diameter of the inflow artery and draining vein to support the high blood flow that is needed in the extracorporeal dialysis circuit.<sup>5</sup> Others have reported a rapid increase in the AVF blood flow rate and diameter that occurs as early as 1 day after

AVF creation and continues to increase progressively over the subsequent few weeks.<sup>6–9</sup> Preoperative

Received February 6, 2015. Accepted April 6, 2016.

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Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org).

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arterial and venous functional properties may modulate the magnitude of these postoperative changes.

The ability of arteries and veins to dilate in response to physiologic stimuli can be assessed noninvasively with several vascular function tests (VFTs). Flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD) assess the capacity of the brachial artery to dilate. FMD measures the increase in brachial artery diameter in response to a sudden increase in blood flow and partly depends on the ability of the endothelium to release the endogenous vasodilator nitric oxide.<sup>10</sup> In contrast, NMD measures the intrinsic ability of the arterial media to respond directly to an exogenous nitric oxide donor and is, therefore, independent of a functional endothelium.<sup>10</sup> Pulse wave velocity (PWV) measures the velocity of arterial blood flow, and it is directly related to arterial stiffness and inversely related to the ability of the artery to dilate in response to increased pressure.<sup>11,12</sup> Carotid-femoral PWV largely provides a measure of stiffness of the aorta, an elastic artery, whereas carotid-radial PWV relates to stiffness of the muscular arteries in the upper extremity. Finally, venous occlusion plethysmography (VOP) measures venous capacitance (CAP; *i.e.*, the ability of the vein to dilate to accommodate the increased blood volume). Preoperative measures of VOP were shown in a small study to predict AVF maturation.<sup>13</sup> It is, therefore, plausible that each of these VFTs predicts the physiologic responses of the AVF (*e.g.*, change in the blood flow rate and luminal diameter) after its creation, but there is a dearth of information in this context. Relationships of preoperative VFTs with postoperative AVF blood flow and diameter could provide insight into the mechanisms underlying these aspects of AVF maturation.

The Hemodialysis Fistula Maturation (HFM) Study is a prospective multicenter cohort study of AVF maturation.<sup>14</sup> Study participants underwent standardized preoperative ultrasounds of the upper extremity arteries and veins and VFTs within 45 days before AVF surgical creation. In this report, postoperative AVF ultrasounds performed at 1 day, 2 weeks, and 6 weeks were used to evaluate the relationships of preoperative functional properties of arteries and veins with subsequent AVF characteristics. We hypothesized that higher FMD and NMD, lower PWV, and higher venous CAP would be associated with greater AVF blood flow rate and diameter after AVF creation.

## RESULTS

Table 1 summarizes baseline demographic and clinical characteristics of the study cohort. The preoperative ultrasound vascular measurements (medians and 15th to 85th percentiles) were as follows: inflow artery diameter of 3.9 mm (2.4–5.0 mm), minimum vein diameter of 3.0 mm (1.7–4.1 mm), and brachial artery flow rate of 62.7 ml/min (37.0–107.3 ml/min). Excluding patients who experienced AVF thrombosis or intervention, the 6-week postoperative ultrasound AVF

**Table 1.** Baseline demographic and clinical characteristics of the study cohort ( $n=602$ )

Baseline Factor	N (%) or Median (15th to 85th Percentiles)
Age, yr	56.4 (40.8–68.5)
Women	180 (30)
Black <sup>a</sup>	264 (44)
On hemodialysis	383 (64)
Diabetes	353 (59)
Peripheral artery disease	91 (15)
Coronary artery disease	156 (26)
Upper arm fistula	459 (76)
Body mass index, kg/m <sup>2</sup>	29.3 (22.8–38.2)
Vascular calcification <sup>b</sup>	265 (44)

<sup>a</sup>Self-reported race was missing for eight subjects, all with upper arm AVFs.

<sup>b</sup>Vascular calcification (on preoperative ultrasound) score  $\geq 1$  on a 0–2 scale.

measurements were as follows: inflow artery diameter of 4.8 mm (3.4–5.9 mm), average vein diameter of 6.2 mm (4.8–8.1 mm), and AVF blood flow of 917 ml/min (426–1628 ml/min). Table 2 summarizes the results of the five preoperative VFTs included in this study, including the 85th and 15th percentiles.

Figure 1 depicts the relationships between the ultrasound outcomes and each VFT predictor variable after adjustment for AVF location, the preoperative ultrasound assessment, and several demographic case mix factors as covariates. Each relationship is normalized to provide estimates of adjusted comparisons in the ultrasound outcomes between the 85th and 15th percentiles of the respective VFT variables to simplify comparison of the strength of the relationships with the ultrasound outcomes across the five VFT factors. The comparisons of the ultrasound outcomes between the 85th and 15th VFT percentiles are expressed as adjusted ratios of the geometric mean levels of AVF blood flow rate and adjusted algebraic differences in mean AVF vein diameter. We used differences for absolute diameters but ratios for blood flow rates, because AVF diameters were symmetrically distributed, whereas AVF flows were positively skewed in the study cohort. Each comparison was made using a mixed effects regression analysis with a random clinical center effect and fixed effects for the VFT predictor variable and the covariates noted above.

The preoperative brachial NMD was positively associated with both the postoperative AVF diameter (Figure 1, left panel) and blood flow rate (Figure 1, right panel). These associations reached statistical significance by the 2-week ultrasound assessment and continued to strengthen at the 6-week ultrasound assessment. Brachial FMD exhibited similar, although slightly less pronounced, relationships with 6-week AVF diameter and blood flow rate. None of the other three VFTs (CAP slope, carotid-femoral PWV, or carotid-radial PWV) exhibited consistent statistically significant relationships with postoperative AVF diameter or blood flow rate, although the 2-week AVF vein diameter exhibited a weak but nominally

**Table 2.** Values for preoperative VFTs for the fully imputed data

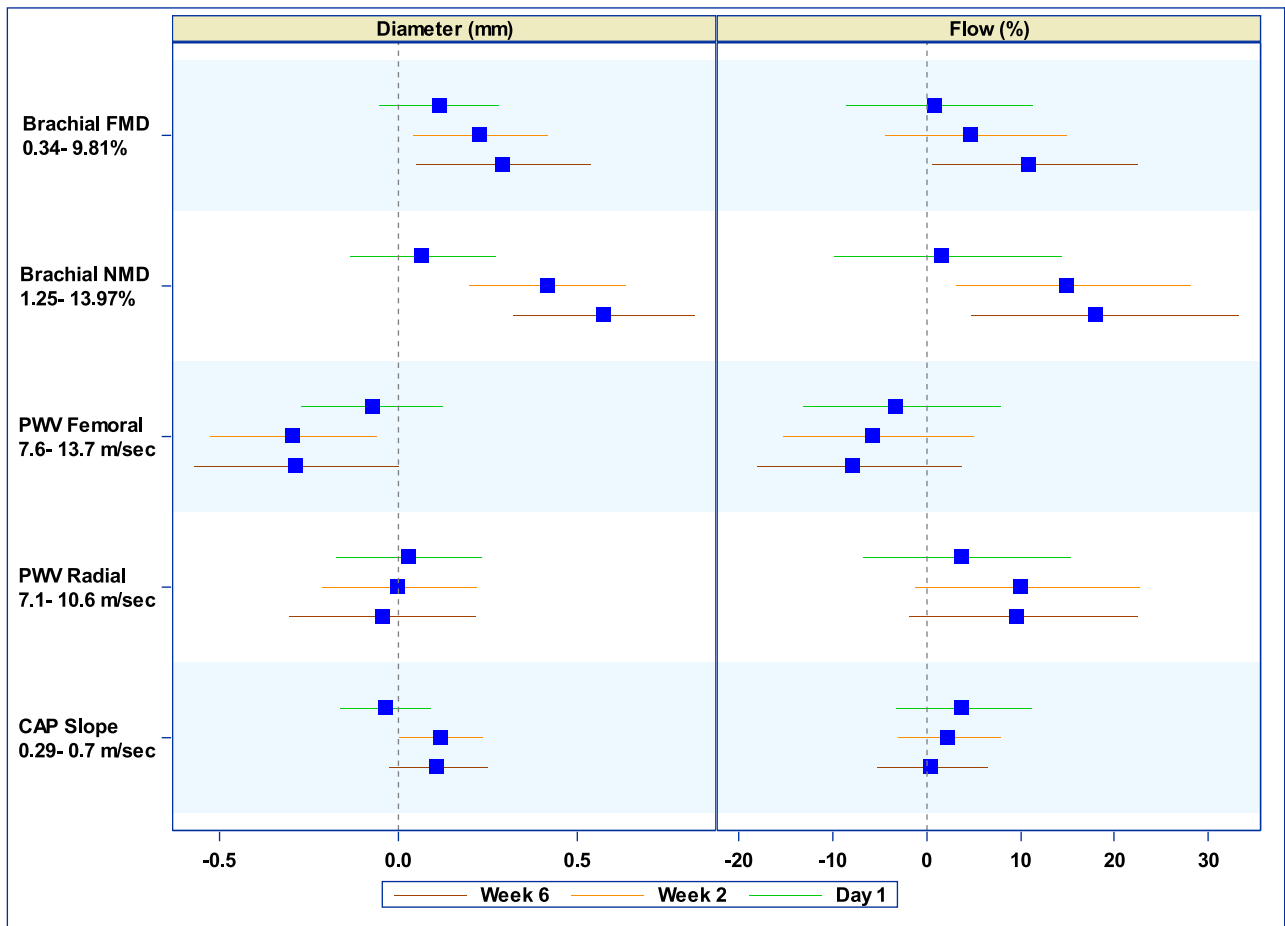
VFT	N of Patients	Mean	SD	Median	15th to 85th Percentiles
Brachial artery FMD, %	549	4.8	5.0	3.9	0.34–9.81
Brachial artery NMD, %	460	7.2	6.3	5.8	1.25–13.97
Carotid-femoral PWV, m/s	448	10.7	3.2	10.0	7.6–13.7
Carotid-radial PWV, m/s	449	8.8	1.7	8.8	7.1–10.6
CAP slope by VOP, %	569	0.53	0.36	0.47	0.29–0.70

Summary statistics are on the basis of observed data only without imputation of missing values.

significant direct association with the CAP slope and an inverse association with carotid-femoral PWV. Very similar results were obtained when each of these analyses was restricted to the subcohort of patients with nonmissing preoperative VFT measurements (data not shown).

10% higher absolute level of brachial FMD, there was an 11.6% (95% CI, 0.6% to 23.9%) higher AVF blood flow rate and a 0.31 mm (95% CI, 0.05 to 0.57 mm) greater 6-week AVF diameter. Qualitatively similar relationships were obtained when the analyses were restricted to subjects with

Tables 3 and 4 provide additional details on the relationships between baseline VFTs and the postoperative AVF diameter and blood flow measurements at 6 weeks. Each 10% higher absolute level of brachial NMD was associated with a 14.0% (95% confidence interval [95% CI], 3.7% to 25.3%) higher 6-week AVF blood flow rate and a 0.45 mm (95% CI, 0.25 to 0.65 mm) greater AVF diameter. Similarly, for each



**Figure 1.** Postoperative AVF diameter and blood flow are associated with the preoperative FMD and NMD. Ratios of mean AVF blood flow rates and differences in mean AVF vein diameters (millimeters) between the 85th and 15th percentiles of preoperative VFT results using mixed effects regression models. Results are adjusted for AVF location, preoperative ultrasound measures (inflow artery diameter, minimum vein diameter, and brachial artery blood flow), and baseline demographics (age, sex, race, and dialysis status). Expressing the results as comparisons between the 85th and 15th percentiles for each VFT factor allows the strength of the displayed relationships to be compared between the different VFT factors. Results are displayed for day 1 (top line; green), week 2 (middle line; orange), and week 6 (bottom line; brown) ultrasounds. The blue squares represent the estimated ratios of mean blood flow rates or mean differences in diameters for VFTs at the 85th and 15th percentiles, and the colored lines are the 95% CIs. Multiple imputation was performed to impute missing vascular function and ultrasound measurements.

**Table 3.** Association of 6-week AVF flow rate with preoperative predictor VFT variables controlled for AVF location, preoperative ultrasound features, and baseline demographics

Predictor Variable	Difference in Blood Flow, %	95% CI	P Value
Brachial FMD per 10% increase	11.6	0.6 to 23.9	0.04
Brachial NMD per 10% increase	14.0	3.7 to 25.3	<0.01
Carotid-femoral PWV per 4-m/s increase	-5.2	-12.2 to 2.5	0.18
Carotid-radial PWV per 4-m/s increase	11.2	-2.0 to 26.1	0.10
VOP per 1% increase in CAP slope	1.2	-12.2 to 16.6	0.87

Preoperative ultrasound features were preoperative inflow artery diameter, minimum vein diameter, and brachial artery flow. Baseline demographics were age, sex, race, and dialysis status. None of the summarized relationships exhibited statistically significant departures from linearity ( $P>0.05$  for evaluation of nonlinearity using cubic spline models). Multiple imputation was used to impute missing vascular function and ultrasound measurements.

nonmissing VFT measurements (Supplemental Appendices 1–3, Supplemental Tables 1–4). Figure 2 depicts the shapes of the relationships of brachial NMD with the 6-week AVF blood flow rate and diameter.

## DISCUSSION

Given that all five preoperative VFTs used in this study assessed vascular functional properties that are of potential relevance to AVF maturation, we hypothesized that each of them would be associated with postoperative changes in AVF blood flow rate and diameter. Consistent with our hypothesis, we observed statistically significant associations of NMD and FMD with both the 6-week postoperative AVF flow rate and diameter, with slightly stronger relationships observed for NMD compared with FMD. Although we had hypothesized that stiffness of the arterial conduit used to create the AVF, as assessed by carotid-radial PWV, would restrict arterial outward remodeling,<sup>15</sup> this study failed to show such a relationship. Although carotid-femoral PWV exhibited a trend for an inverse relationship with 6-week AVF diameter, neither carotid-femoral PWV nor carotid-radial PWV exhibited statistically significant relationships with AVF blood flow. Finally, although we observed a weak inverse relationship of VOP with vein diameter at 2 weeks, we did not observe a consistent relationship of VOP with AVF blood flow or diameter across the three consecutive postoperative assessments.

FMD and NMD measure the ability of arteries to dilate in response to physiologic and direct biochemical stimuli, re-

spectively. Thus, one might expect patients with higher FMD and NMD values to have higher postoperative AVF blood flow rates and diameters. FMD measures endothelium-dependent arterial responsiveness to hyperemia. After release of the BP cuff, blood flow increases in response to local vasodilators released during ischemia, and this increased blood flow results in increased shear stress on the arterial wall, which in turn, stimulates the release of nitric oxide from the endothelium and subsequent dilation of healthy arteries. FMD was originally considered to result almost exclusively from shear stress-induced endothelial production of nitric oxide.<sup>16</sup> Because the endothelium is the primary source of nitric oxide in the vasculature, FMD was considered a marker of endothelial function, with attenuated FMD reflecting a diseased endothelium. More recent data, however, suggest that FMD reflects not only nitric oxide production<sup>17,18</sup> but also, the arterial response to other vasodilatory factors, such as prostaglandins, adenosine, and endothelium-derived hyperpolarizing factor.<sup>19–21</sup>

In contrast to FMD, NMD measures arterial dilation after exogenous administration of nitroglycerin, an exogenous nitric oxide donor. Thus, NMD assesses endothelium-independent vasodilation and reflects both physical properties of the arterial wall and arterial smooth muscle function. One would, therefore, expect greater vasodilatory responses to exogenous nitric oxide to translate into higher postoperative AVF blood flow rate and diameter, and this was, in fact, observed in this study (Figures 1 and 2, Tables 3 and 4).

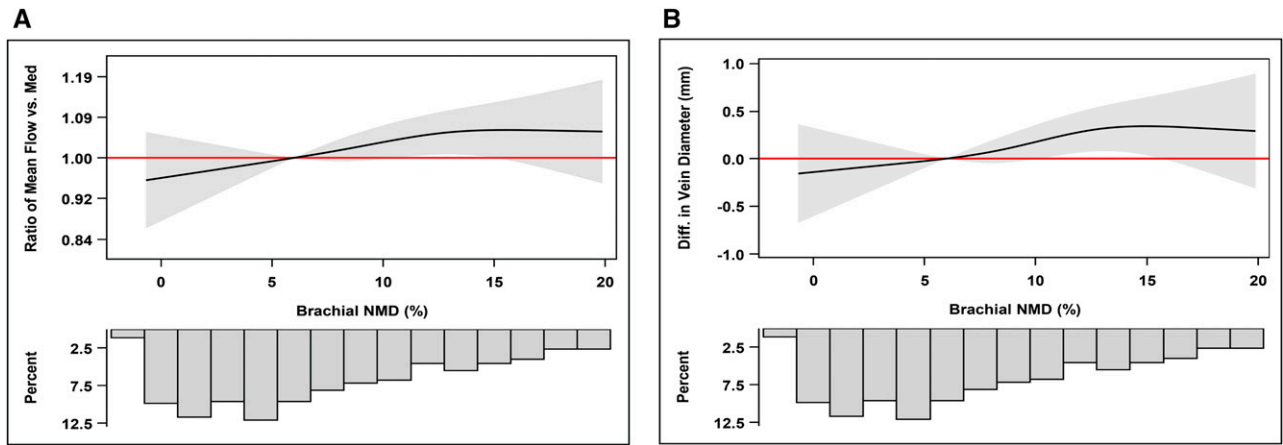
PWV assesses arterial stiffness. Because stiffer vessels dilate less, one would expect negative associations of changes in postoperative AVF flow rate and diameter with preoperative

**Table 4.** Association of 6-week AVF diameter with preoperative predictor VFT variables controlled for AVF location, preoperative ultrasound features, and baseline demographics

Predictor Variable	Difference in Diameter, mm	95% CI	P Value
Brachial FMD per 10% increase	0.31	0.05 to 0.57	0.02
Brachial NMD per 10% increase	0.45	0.25 to 0.65	<0.001
Carotid-femoral PWV per 4-m/s increase	-0.19	-0.37 to -0.00	0.05
Carotid-radial PWV per 4-m/s increase	-0.05	-0.35 to 0.25	0.76
VOP per 1% increase in CAP slope	0.27	-0.06 to 0.61	0.11

Multiple imputation was applied to impute missing vascular function and ultrasound measurements.

Preoperative ultrasound features were preoperative inflow artery diameter, minimum vein diameter, and brachial artery flow. Baseline demographics were age, sex, race, and dialysis status. Multiple imputation was used to impute missing vascular function and ultrasound measurements.



**Figure 2.** A greater preoperative NMD is associated with a greater 6-week postoperative AVF blood flow and diameter. (A) The y coordinates on the solid curve provide the ratio of the adjusted geometric mean 6-week AVF blood flow rate at the indicated brachial NMD level to the adjusted geometric mean blood flow rate at the median brachial NMD, which is used as the reference. (B) The y coordinates provide the difference between the adjusted mean 6-week AVF vein diameter at the indicated brachial NMD and the adjusted mean AVF vein diameter at the median brachial NMD reference. Analyses are adjusted for AVF location, baseline ultrasound measurements, and baseline case mix covariates. Multiple imputation was performed to impute missing vascular function and ultrasound measurements. The shaded regions indicate pointwise 95% CIs. Histograms below the curves show the distribution of NMD values in the study cohort.

PWV. Carotid-femoral PWV focuses on the stiffness of the central aorta, an elastic artery. Carotid-femoral PWV might be relevant to AVF maturation, because central aortic stiffness is an important determinant of the pulsatility and mechanical forces acting on the newly created AVF. In contrast, the carotid-radial PWV measures the stiffness of more peripheral (axillary, brachial, and radial) arteries that are muscular arteries. Notably, both PWV techniques are limited, because they represent indirect measures of arterial stiffness and are influenced by the collective stiffness of several different arteries that may differ in their stiffness.

Whereas NMD, FMD, and PWV each measure the functional properties of arteries, VOP assesses the ability of veins to dilate in response to physical forces, namely blood engorgement by cuff occlusion of the arm. A previous study of 17 patients found a positive association of AVF maturation with preoperative CAP assessed by VOP.<sup>13</sup> VOP has been the gold standard for measuring limb blood flow for many years.<sup>22</sup> However, it is not highly reliable for measuring the compliance of large veins for several reasons. First, it estimates the overall compliance of the entire venous system in the limb rather than only the compliance of the large veins, which are the vessels of interest in AVF maturation. Second, it does not directly measure the change in venous volume but rather, the sum of changes in both intravascular and extravascular volumes in the arm.<sup>23</sup> Third, the relationship between cuff pressure and actual venous pressure may differ in patients with increased resting venous pressure.<sup>24,25</sup> These limitations of VOP are balanced by its noninvasive nature, relative simplicity, and long track record. To more accurately investigate the relationship between the mechanical properties of the vein used for AVF creation and postoperative AVF remodeling, direct measurement of the

vein of interest would be necessary. For example, the elasticity imaging technique using high-resolution ultrasound speckle tracking, which has been tested on a patient with CKD in a proof of concept study,<sup>26</sup> might be used for this purpose.

This study has several strengths, including the large number of patients from multiple clinical centers, the inclusion of both forearm and upper arm AVFs, the utilization of multiple types of VFTs, and the assessment of both arteries and veins as well as the standardized central training and quality assurance for the VFTs and ultrasound techniques across centers.

This study has three notable limitations. First, the process of associating two AVF ultrasound outcome measures (AVF blood flow rate and diameter) in separate models with each of five VFT predictors at three time points for a total of 30 (2×3×5) 5%-level hypothesis tests is vulnerable to false positive results as a consequence of multiple comparisons. However, even after conservative Bonferroni adjustments for 30 comparisons, the *P* value for the relationship of brachial NMD with 6-week AVF diameter remained statistically significant. The observation of consistent relationships of brachial NMD and FMD with AVF diameter and blood flow rate across two of the three ultrasound assessments (2 and 6 weeks) also alleviates this concern. Second, the proportion of missing VFT measurements was relatively high (Table 2). Our use of a comprehensive model for multiple imputation and the consistency of our results between analyses incorporating imputed values for missing VFT measurements and analyses restricted to nonmissing VFT measurements suggest that the reported relationships of brachial NMD and FMD with the ultrasound outcomes are unlikely to be the result of bias because of missing data. Third, even after multiple imputation, it was necessary to restrict

regression analyses involving postoperative ultrasound measurements to ultrasound assessments planned to occur before patient death or AVF thrombosis to avoid interpretational paradoxes. However, the proportions of subjects excluded for this reason were relatively small (ranging from 2% to 8%) (Supplemental Table 1).

In summary, in this multicenter observational study of new AVFs, two preoperative VFTs, arterial NMD and FMD, were associated with the postoperative changes in AVF blood flow rates and vein diameter after controlling for AVF location, preoperative vascular diameters and blood flow rates, and baseline demographics. The relationship of NMD and FMD with postoperative AVF measurements suggests a role of preexisting functional properties of arteries in the early remodeling of AVF after its creation. This observation raises the possibility that pharmacologic interventions to improve arterial function in patients with CKD may improve AVF maturation.

## CONCISE METHODS

### Study Design

The HFM Study enrolled 602 patients identified at the time that they were scheduled for AVF creation at seven clinical centers. Details of the overall study design and its rationales have been published previously.<sup>14</sup> Patients were eligible if they were currently on maintenance hemodialysis or anticipated to require hemodialysis within 3 months; were scheduled for a single-stage AVF creation surgery in the upper extremity; were <80 years of age if they had not yet started dialysis; had a life expectancy of  $\geq 9$  months; and were willing and able to comply with the study procedures. Furthermore, to qualify for the study, patients were required to complete a preoperative vascular ultrasound and testing in at least two of the following three preoperative VFT categories: arterial dilation as assessed by FMD and/or NMD, arterial stiffness as assessed by carotid-femoral and/or carotid-radial PWV, and venous CAP as assessed by VOP. The participants underwent standardized postoperative AVF ultrasound at 1 day, 2 weeks, and 6 weeks to measure AVF blood flow rate and draining vein diameter averaged over several locations along its length.<sup>27,28</sup>

### Brief Overview of the VFTs

The clinical site personnel were trained by the HFM Study Vascular Function Core to perform the VFTs using standardized protocols. Core staff analyzed the brachial artery images transmitted by the clinical centers to calculate the FMD and NMD (both reported as percentages of the baseline value). The individual VFT tests are summarized below, and detailed information is provided in Supplemental Appendix 1. All tests were obtained within 45 days before the AVF creation surgery. Tests were performed in the order given below on the arm to be used for the AVF creation unless a patent AVF was present in that arm.

### VOP

The forearm volume was measured using a strain-gauge plethysmography device during application of an upper arm BP cuff at increasing

but subsystolic pressures. Venous CAP slope was estimated from the volume-pressure relationship and expressed as a percentage increase in volume per millimeters of mercury.

### PWV

Carotid-femoral and carotid-radial PWVs were determined using the SphygmoCor Device (AtCor Medical), with velocity expressed as meters per second. Tonometry signals were obtained at the locations of the carotid, femoral, and radial pulses. Measured distances of each pulse from the sternal notch were used to calculate pulse wave propagation distances.

### FMD

The brachial artery diameter was measured by ultrasound at baseline. A BP cuff was inflated on the upper arm to a suprasystolic pressure that was sustained for 5 minutes, and the brachial diameter measurement was repeated 55–65 seconds after releasing the cuff. FMD was calculated as the percentage change in arterial diameter from baseline.

### NMD

The brachial artery diameter was measured at baseline and again, 3 minutes after administration of 0.4 mg sublingual nitroglycerin. NMD was calculated as the percentage change in arterial diameter from baseline.

## Statistical Analyses

### Missing Data

Logistic and other challenges prevented performance of complete VFT testing in all 602 study participants. The numbers of patients with nonmissing VFT measurements ranged from 448 (74%) for carotid-femoral PWV to 569 (95%) for VOP. Some patients also had missing ultrasound measurements, in part because of attrition of the cohort caused by patient death and AVF thrombosis and in part because of intermittently missed ultrasound measurements (Supplemental Appendix 2, Supplemental Table 1). In addition, because our objective was to describe the role of vascular function in the natural history of AVF development, ultrasound measurements after AVF interventions were deleted before subsequent analyses. To minimize risk of bias caused by missing data, we performed multiple imputation to impute missing VFT measurements as well as missing ultrasound measurements for visits scheduled before AVF thrombosis or patient death. Missing ultrasound values after death and thrombosis were not imputed to avoid conceptual paradoxes; hence, the results pertaining to ultrasound outcomes at the day 1, week 2, and week 6 visits pertain to the subcohorts of survivors without thrombosis before these visits. In sensitivity analyses, the regression analyses relating the ultrasound outcomes to each preoperative VFT were repeated after restricting to patients with nonmissing VFT measurements. Supplemental Appendix 2 and Supplemental Table 2 show tabulations of the numbers of subjects affected by missing data and a detailed description of the multiple imputation procedure.

### Statistical Analyses Relating Ultrasound and VFT Measures

We fit separate generalized linear mixed effects regression models to relate each of the five baseline vascular function variables to the average

AVF draining vein diameters or AVF blood flow rates at the 1-day, 2-week, and 6-week ultrasound examinations after AVF placement (i.e.,  $5 \times 2 \times 3 = 30$  models; corresponding to each combination of the five VFT measurements, the two ultrasound outcomes, and the three postoperative time points). Each of the 30 regression models was fit after adjusting for AVF location (forearm versus upper arm), preoperative ultrasound measurements (inflow artery diameter, minimum vein diameter, and brachial artery flow), and baseline demographics (age, sex, race, and dialysis status).

Additional models with natural cubic splines with four equally spaced knot points were used to evaluate linearity assumptions in the VFT measures and depict the shape of the relationships between the ultrasound outcomes and the VFT predictors after adjustment for the same covariates listed above. Sensitivity analyses were performed to test for interactions between VFT parameters and fistula location (upper arm versus forearm). Technical details of the regression models are provided in Supplemental Appendix 3.

All analyses were performed in SAS, version 9.4 (SAS Institute Inc., Cary, NC). *P* values and 95% CIs are reported on a comparison-wise basis without formal adjustment for the conduct of multiple analyses. Hence, results are interpreted as exploratory, recognizing the risk of type 1 error because of multiple hypothesis tests.

## ACKNOWLEDGMENTS

The Hemodialysis Fistula Maturation Study is funded by the National Institute of Diabetes, Digestive and Kidney Disease grants U01DK066597, U01DK082179, U01DK082189, U01DK082218, U01DK082222, U01DK082236, and U01DK082240.

Portions of this manuscript were presented at the American Society of Nephrology Kidney Week Meeting in Philadelphia, Pennsylvania (November 12–16, 2014).

Study group members are listed in ref. 14.

## DISCLOSURES

M.A. is a consultant for Cor-Medix and Gore. L.M.D. is a consultant for Proteon Therapeutics. A.K.C. is a DSMB member of TVA Medical, Inc. J.S.K. is the chair of the Data Safety and Monitoring Board for Proteon Therapeutics.

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- See related editorial, “Predicting the Functionality and Form of a Dialysis Fistula,” on pages 3508–3510.
- This article contains supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2015020141/-/DCSupplemental>.