The Spectrum of Hand Dysfunction After Hemodialysis Fistula Placement

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Introduction: Contemporary dogma has classically attributed hand dysfunction following hemodialysis arteriovenous fistula (AVF) placement to regional ischemia. We hypothesize that hemodynamic perturbations alone do not entirely explain the postoperative changes in hand function and, furthermore, that various elements of hand function are differentially affected following surgery.

Methods: Bilateral wrist and digital pressures and upper extremity nerve conduction tests were recorded preoperatively and at 6 weeks and 6 months following upper extremity AVF construction in 46 patients. Concurrently, biomechanical tests were administered to evaluate multiple limb functional domains, including grip strength, dexterity, sensation, and perception of hand function.

Results: Mean participant age was 59 $\pm$ 14 years (75% male), and 48% were on hemodialysis at the time of access placement. Of the participants, 69% had a brachial-based AVF, and the remainder had radial-based accesses. Six weeks following AVF placement, a significant decrease in access-side digital pressures was observed, with only partial recovery at 6 months ($P < 0.0001$). Grip strength was significantly worse in the access-side limb ($P = 0.0003$), and the Disability of Arm, Shoulder and Hand (DASH) questionnaire score substantially worsened postoperatively ($P = 0.06$). Digital sensation and limb dexterity did not differ between limb sides ($P > 0.1$) or change significantly over time ($P > 0.1$). Principal component analyses demonstrated that nerve conduction parameters tended to track the biomechanical parameters, yet both were relatively independent of the hemodynamic parameters.

Discussion: Our findings suggest that ischemia alone does not completely explain access-related hand dysfunction and that future study is needed to elucidate alternative mechanisms.

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Approximately 400,000 patients currently receive hemodialysis (HD) in the United States, and 30% to 60% have some degree of hand disability.[1,2] The clinical spectrum of impairment that occurs after autogenous arteriovenous HD access (AVF) placement ranges from subtle alterations in sensation and coordination to paraparesis and gangrene.[3] Contemporary dogma has classically attributed post-AVF hand dysfunction to regional access-related hand ischemia (ARHI). In fact, a reduction in limb pressures does occur in 60% to 80% of patients with brachial-based access procedures.[4] However, despite the prevalence of limb hemodynamic changes, only 5% to 10% of patients have clinically significant neuromotor dysfunction requiring remediation after hemoaccess surgery. Hence, hemodynamic perturbations appear to be poor predictors of significant post-AVF hand disability.[4–6] Moreover, up to 20% of patients undergoing distal revascularization and interval ligation for ARHI experience persistent neurological complaints despite restoration of limb hemodynamics.[7]

The lack of direct correlation between changes in hand perfusion and rates of clinically apparent hand dysfunction after AVF surgery hints at the presence of additional influences, in addition to the direct effects of ischemia, which contribute to postoperative limb disability. Potential factors include inflammation, skeletal muscle cell dysfunction, blood vessel reactivity, surgical trauma and uremic polyneuropathy,[8]

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We hypothesize that hemodynamic perturbations alone do not explain the spectrum of disability after AVF placement and that various aspects of biomechanical hand function are differentially affected following surgery. The primary aims of this study are to characterize the temporal changes in both hemodynamics and hand function after AVF placement and to examine the interconnectedness of these domains.

MATERIALS AND METHODS

This study was approved by the University of Florida institutional review board, and informed consent was obtained for all patients (IRB#140-2013, IRB#556-2009).

Study Design

A total of 46 patients with end-stage renal disease were prospectively enrolled at the University of Florida between 2012 and 2015. Adult patients with a life expectancy ≥9 months were eligible for enrollment if creation of a single- or 2-staged autogenous upper arm fistula was planned and they were currently on HD or expected to start chronic HD within 3 months of surgery. Demographics, comorbidities, prior access history, hand dominance, operative details, and postoperative outcomes were all prospectively entered into a database. Patients were evaluated preoperatively, as well as 6 weeks and 6 months postoperatively.

Operative Procedure

All patients underwent preoperative noninvasive upper extremity arterial and venous imaging, and the optimal configuration for a native AVF was selected based on a previously published protocol[9] and guidelines.[10–12] The access was always placed on the side with the most suitable vein, regardless of patient handedness. Radiocephalic autogenous distal forearm, brachial-cephalic upper arm, and the first stage of planned 2-stage brachial-basilic fistula operations were routinely performed under local anesthesia with conscious sedation. No patient received an upper extremity regional anesthetic block. Basilic vein transposition was completed using general anesthesia. Follow-up time for staged basilic vein transposition procedures began with the initial creation of the nontransposed fistula.

Biomechanical Function Testing

Hand function was assessed concurrently with hemodynamic measurements. An array of tests was administered to evaluate multiple domains of hand function including grip strength, dexterity, sensation, and perception of limb function.

Grip Strength

A modified Groningen Elderly test protocol[13] was used, and the highest value after 3 attempts using a Smedley Digital Hand Dynamometer (Model 12-0286, Baseline Evaluation Instruments, China) was recorded. The patient was instructed to rest the hand at his or her side and was given 1 practice trial, followed by 3 attempts with 30-second rest intervals.

Dexterity

The Purdue Pegboard test is a validated tool that assesses fine motor coordination and dexterity.[14] A patient's score equaled the average among 3 consecutive trials of the number of pegs properly placed in the pegboard (Model 3200, Lafayette Instrument, Lafayette, IN) within a 30-second period.

Sensation

First- and fifth-digit light touch was assessed using standardized Semmer-Weinstein Monofilament testing (300, 4.0, 2.0, 0.4 and 0.07 g, Tactile Monofilaments, Baseline Evaluation Instruments, Fabrication Enterprises Inc., White Plains, New York). With the patient's eyes closed, the examiner touched the ventral surface of the fingertip with the monofilament 3 times at 1.5-second intervals. The applications were randomized, and the smallest monofilament sensed was recorded. The final raw dataset was transformed so that 1 corresponded to the 300-g monofilament (worst sensation) and 5 corresponded to the 0.07-g monofilament (best sensation).

Hand−Limb Function Perception

Patient perception of limb function and symptomatology with routine daily tasks was evaluated using the Disability of Arm, Shoulder and Hand (DASH) questionnaire (Form S1). This is a validated survey that assesses general limb disability.[15] The questionnaire consists of 30 questions answered on a 5-point Likert scale, with 1 corresponding to the most favorable clinical response.

Hemodynamic Measurements

At each time point, the following systolic pressures were measured bilaterally: distal first and fifth digits, radial and ulnar arteries at the wrist, and the brachial artery in the antecubital fossa. Pressures were obtained using inflatable cuffs and 4- to 8-MHz Doppler probes (Parks Flow Lab, Aloha, OR), which were placed over the artery at a 45° to 60° angle to the vessel's expected longitudinal axis. The cuff was inflated 20 to 30 mm Hg beyond the audible Doppler signal and deflated automatically, and systolic pressure was documented as the first consecutive audible Doppler signal.

Preoperatively, the higher brachial pressure was used as the normalizing value when calculating finger- and wrist-brachial indices (WBI). However, only non−access-side brachial pressures were available postoperatively to avoid compression of the newly constructed fistula. The WBI was calculated by dividing the higher of the radial and ulnar artery measurements by the brachial pressure. Similarly, the presence of a radiocephalic fistula precluded wrist pressure measurements; only digital pressures were recorded in these patients. Patients were required to refrain from taking their antihypertensive medications during the 24-hour period prior to the preoperative visit so as not to confound the results of arterial flow−mediated dilation studies, which were performed at the preoperative time point only. At subsequent time points, patients had resumed taking all medications.

Nerve Conduction Studies

Median and ulnar sensory and motor nerve conduction studies were performed concurrently with hemodynamic and functional tests to analyze respective latencies, amplitude, conduction velocity, and F-wave data with the use of Natus Neurology Viking EDX (Nicolet, Middleton, Wisconsin) and Viking Quest units (Nicolet, Middleton, Wisconsin), preset with standard filter settings. Surface skin temperature was recorded over the first dorsal interosseous muscle.

Statistical Analyses

Linear mixed-effects models were used to assess the effects of limb side (access/nonaccess), assessment time (preoperatively/6 weeks/6 months) and their interactions on hemodynamic and biomechanical parameter response means. To account for within-patient correlation of responses over time and between limb sides, patient was modeled as a random effect. Four potential modifiers of the effects of limb side, time, and their interaction were also included in these models: status of the AVF limb with respect to hand dominance (AVF limb dominant/AVF limb non-dominant); AVF configuration (brachial/radial); preoperative HD status (on HD/not on HD); and diabetes mellitus (DM) status (DM/no DM). Each potential effect modifier was allowed to interact with the effects of limb side, time, and their interaction. To preclude the risk of model overfitting, interactions among the effect modifiers were not considered. To be included in the analysis of a given parameter, patients were required to have at least 2 nonmissing responses in the time profile of each limb side. This pattern of missingness is efficiently accommodated in mixed effect models. Subcomparisons of response means were selectively performed in instances in which results would be of particular clinical interest.

No clear standard exists for handling the potential problem of multiple comparisons within a model, yet the importance of reducing type I error through some correction method is prudent. We chose a logical adjustment strategy that satisfied the need to establish increased stringency yet still preserved the discovery aspect of our study. Our model tested a total of 45 effects: 10 effects for each of 4 biomechanical tests and 5 effects for 1 test (DASH). Setting our α level at 0.022 predicts the occurrence of just less than a single (0.99) expected false rejection of the null hypothesis for the entire model, which is a reasonable standard.[16] In contrast, the conventional threshold of 0.05 predicts 2.25 false-positive results for our particular model.

PCA was used to explore associations among hemodynamic, hand function, and nerve conduction parameters. PCA is a useful tool for identifying and visualizing associations among variables and among experiments within a complex, multidimensional dataset.[17] The data are deconstructed and characterized by a set of orthogonal eigenvectors chosen such that each vector lies along the direction of maximal remaining dataset variance. Corresponding eigenvalues indicate the relative degree of data variation explained by each vector.[18] By reducing our multidimensional dataset down to 2 dominant components, strong patterns of association among the original variables and among patients were revealed. To attain a sufficiently complete dataset, the variables "wrist pressure" and "WBI" were excluded from this portion of the analysis, because the first 26 patients were enrolled before these measurements were included in the protocol. Data from 31 patients were included in the PCA of combined hemodynamic and biomechanical parameters. In concert with ongoing research on AVF and nerve conduction, we also carried out a PCA on the first principal components from separate PCAs of access-side biomechanical, hemodynamic, and nerve conduction study parameter responses, to assess gross associations among these 3 sets of parameters.

Correlations between grip strength and patient perception of hand weakness were determined by correlating the patient's response (Likert scale, 1−5) to DASH question 27, "Rate the severity of weakness in your arm, shoulder or hand within the last week," with his or her measured grip strength. Spearman's rho values were calculated in SPSS 22 software (IBM Corp., Armonk, NY). All other analyses were performed with SAS and R statistical software package (V.3.0.2; Vienna, Austria).

RESULTS

Patient Characteristics and Operative Details

A total of 46 patients were enrolled, with a mean age of 59 ± 14 years. The majority were male (75%), and the most prevalent comorbidities were hypertension (98%) and diabetes (70%). Nearly half (46%) were undergoing chronic HD at the time of operation, although the duration was less than 6 months in the majority (67%) of cases (Table 1).

AVF configurations were as follows: 43% brachial-cephalic upper arm direct access (n = 20), 31% radial-cephalic direct wrist access (n = 14), and 26% brachial-basilic upper arm transposition (n = 12). The fistula was placed in the dominant arm in almost half of the cases (48%). Several patients (9%) had a prior access attempt, 3 on the ipsilateral and 1 on the contralateral arm. Twenty-six (56%) subjects underwent a remedial access procedure (excluding planned second-stage basilic vein transposition) during follow-up (mean 6.2 ± 3.2 months). One patient had overt ARHI and underwent access ligation (Table 1).

Table 1. Demographics, comorbidities, and access outcomes (N = 46)

Variable	n (%)[a]
Age, mean ± SD, yr	59 ± 14
Male	36 (75)
Race	
White/Caucasian	27 (59)
Black/African American	18 (39)
Other	1 (2)
Comorbidities	
Hypertension	45 (98)
Diabetes	32 (70)
Hyperlipidemia	27 (59)
Congestive heart failure	14 (30)
Etiology of renal disease	
Diabetic nephropathy	15 (33)
Hypertensive nephropathy	7 (15)
Other diagnosis	5 (10)
Glomerulonephritis	3 (7)
Idiopathic	16 (35)
Duration of hemodialysis at time of surgery	
Not on hemodialysis	24 (52)
<6 months	14 (30)
6–12 months	4 (9)
>12 months	3 (7)
Peritoneal dialysis	1 (2)
Prior access surgery history	
None	42 (91)
One	4 (9)
Access configuration	
Brachiocephalic	20 (43)
Radiocephalic	14 (31)
Brachiobasilic: 1-stage	8 (17)
Brachiobasilic: 2-stage	4 (9)
Access on dominant limb side	22 (48)
Successful access cannulation	32 (70)
Access failed/abandoned	6 (13)
Patent access, patient not yet on HD	5 (10)
Access not utilized[b]	3 (7)

HD, hemodialysis.
[a]Data are number (%) unless otherwise specified.
[b]Reasons include the following: access too painful for cannulation (n = 1), access not mature at time of study analysis (n = 1), access abandoned due to access-related hand ischemia (n = 1).

Biomechanical Changes in Hand Function Following AVF

An array of tests focusing on grip strength, dexterity, and sensation was administered preoperatively and at 6 weeks and 6 months postoperatively. Among these functional tests, grip strength showed the greatest difference between the access and nonaccess limbs, with reduced strength seen in the access hand at all time points (side effect $P = 0.0003$) (Figure 1a). DASH scores, a composite measure of patient perceived hand dysfunction, demonstrated progressive worsening postoperatively, although this failed to reach statistical significance (time effect $P = 0.06$) (Figure 1b). In contrast, neither digital sensation nor limb dexterity was significantly affected (side effect $P > 0.1$) (Figure 1a). Mean values for all biomechanical parameters in the access and nonaccess limb are highlighted in Table S1.

Correlating Perception and Limb Biomechanics

The patient's perceived limitation of the reduced grip strength was evaluated by correlating measured grip strength with the patient's response to question 27 on the DASH questionnaire, which assessed functional weakness in his or her arm, shoulder or hand. Prior to surgery, no correlation was observed between grip strength and the reported degree of limb weakness (Spearman's rho = −0.017, $P = 0.92$) (Figure 2a). However, 6 weeks postoperatively, patients with lower measured grip strengths tended to report greater degrees of hand weakness (Spearman's rho = −0.44, $P = 0.004$) (Figure 2b). This correlation remained strong at 6 months (Spearman's rho = −0.48, $P = 0.006$) (Figure 2c).

Subgroup Analysis

Due to the known association of HD with altered hand function,[19] cohorts were partitioned by HD status at the time of surgery. In advance of AVF placement, operative-side Purdue Pegboard performance, a measure of manual dexterity, was not significantly different between patient groups. However, although patients not on HD demonstrated the expected improvement in performance, which is generally seen with repeated testing, preoperative HD patients demonstrated no improvement in their dexterity over time (P; HD*time, access sides only = 0.009) (Figure 3), suggesting an impaired ability for adaptation to the new postoperative environment.

The relationship between the side of access placement (i.e., access on dominant limb vs access on nondominant limb) and biomechanical function was explored. Grip strength, Purdue Pegboard performance, and thumb sensation were all significantly

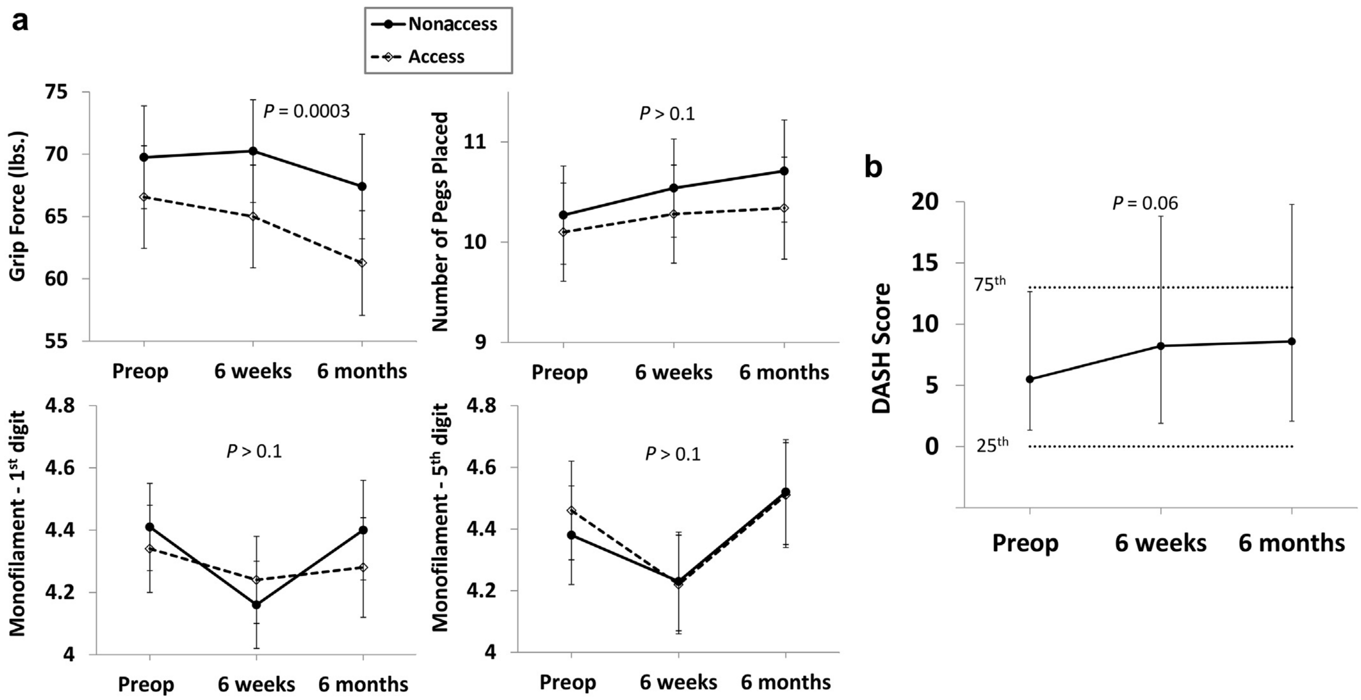

Figure 1. Comparison of limb functionality between sides. (a) Grip strength in the access-side limb was significantly weaker than that in the nonaccess-side limb (side effect, $P = 0.0003$). In contrast, neither Purdue Pegboard performance nor digital sensation was significantly different between sides (side effect, $P > 0.1$). (b) Disability of Arm, Shoulder and Hand (DASH) score showed a strong trend of progressive worsening, demonstrating borderline statistical significance (time effect, $P = 0.06$). The 25th and 75th percentile scores for healthy 50- to 59-year-old men are shown for comparison. Scoring for the DASH questionnaire is oriented so that a lower score corresponds to better limb function.

different between these 2 patient cohorts with respect to limb side (P; dominance* side effect = 0.004, 0.0009, and 0.04, respectively) (Figure S1). The interaction between access configuration and side (configuration*side) was not significant for any biomechanical test, nor was the interaction between diabetes and side (DM*side). Not surprisingly, diabetic patients performed worse on all tests compared to their nondiabetic counterparts, but this effect was independent of both limb side and time.

Hemodynamic Perturbations

Coincident with functional testing of the hand, hemodynamic measurements were taken to assess the perfusion pressures at the wrist and digits. Access-side digital pressures decreased significantly after surgery, with only modest recovery by 6 months. The nonaccess-side digital pressures remained relatively stable, resulting in significant pressure differences between the access and nonaccess limbs over time (side*time effect $P < 0.0001$) (Figure 4). Similar

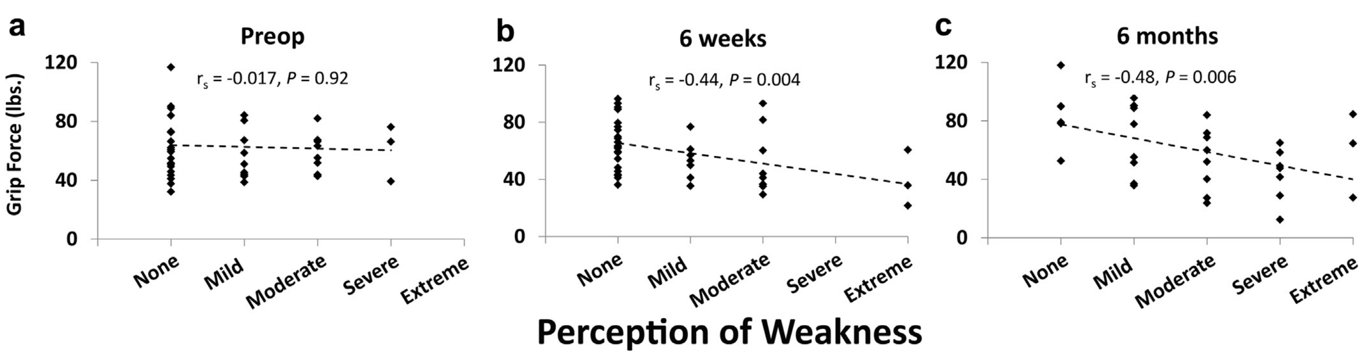

Figure 2. Correlation between the perception and demonstration of limb weakness. Each patient's response to Disability of Arm, Shoulder and Hand (DASH) question 27, "Rate the severity of weakness in your arm, shoulder or hand within the last week," on a 5-point Likert scale was compared to the patient's measured access limb grip strength. (a) Prior to surgery, no correlation existed between grip strength and reported degree of limb weakness (Spearman's rho $= -0.017$, $P = 0.92$). (b) Six weeks after surgery, a moderate inverse correlation between the reported degree of weakness and measured grip strength emerged (Spearman's rho $= -0.44$, $P = 0.004$). (c) This correlation remained strong at 6 months (Spearman's rho $= -0.48$, $P = 0.006$).

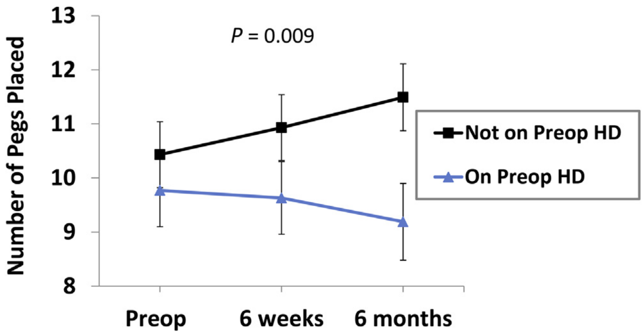

Figure 3. Effect of preoperative hemodialysis status on limb function. Access-side dexterity, measured by Purdue Pegboard performance, was similar prior to surgery between patient groups. However, although a trend of progressive functional improvement is apparent in the nonhemodialysis group, the preoperative hemodialysis group demonstrated no improvement (HD*time, access sides only $P = 0.009$). HD, hemodialysis; Preop, preoperative.

time-dependent changes occurred across all hemodynamic measurement domains, including indexed and nonindexed wrist and digit pressures, reaching similar degrees of significance (Table S2).

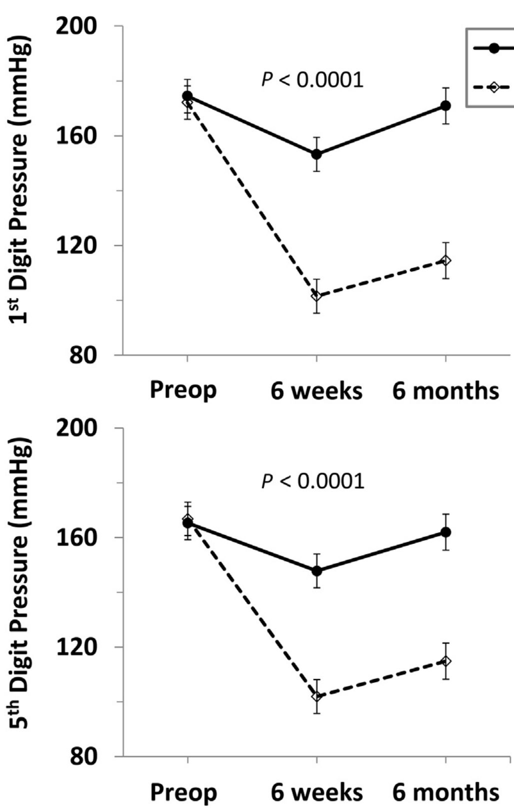

Figure 4. Digital hemodynamic changes following surgery. Access-side first and fifth digital pressures decreased substantially following surgery, with only a modest partial recovery by 6 months. In contrast, the effect of surgery on nonaccess-side digital pressures was significantly less dramatic (side*time effect $P < 0.0001$). Pre-op, preoperative.

Associations Between Hemodynamic and Biomechanical Changes

Central to our analysis was the hypothesis that reduced perfusion was the major (but not sole) driver of functional impairment following access placement. PCA was used to evaluate these relationships in this complex, multidimensional data set. Including the hemodynamic and biomechanical measurements from the access side limb, PCA identified 2 principal components (PCs) that accounted for 77% of the data set's variance (PC1, 46%; PC2, 31%). Moderate clustering of scores by time along the first PC reflects the significant and nearly uniform temporal changes in all hemodynamic parameters in the access limb (Figure 5a). In contrast, a scores plot from the nonaccess side failed to exhibit time-dependent clustering, reflecting the limited hemodynamic changes in nonoperative limbs (Figure 5a). No temporal patterns of variation among all biomechanical tests were sufficiently extreme in magnitude or collectively unidirectional to produce a time-dependent shift across the second PC in either limb (Figure 5a).

The PCA access-side loading plots clearly demonstrated that all hemodynamic variables contributed substantially to the first PC, and therefore account for the majority of the variability in the dataset. However, these hemodynamic variables contributed very minimally to the second PC. The biomechanical tests showed a converse pattern of component loading. Such orthogonality indicates that the variation among hemodynamic measures is relatively independent of the variation seen among biomechanical measures. The very tight clustering of hemodynamic variables reflects their nearly uniform time-dependent changes, whereas looser clustering of the biomechanical tests underscores the higher postoperative variability seen among the biomechanical parameters (Figure 5b).

Scores plots from PCA of all access-side hemodynamic and biomechanical variables failed to show any spatial separation between patient subgroups when partitioned by 3 of the 4 subgroup factors (AVF configuration, preoperative HD status, and AVF side in relation to hand dominance). This succinctly demonstrates the lack of any consistent differences among either the hemodynamic or biomechanical variables between the subgroups within each plot. However, when patients were categorized by diabetes status, moderate spatial separation is seen along the second PC, reflecting diabetic patients' consistently worse performance on all biomechanical tests compared with the nondiabetic cohort, irrespective of time and limb side (Figure S2).

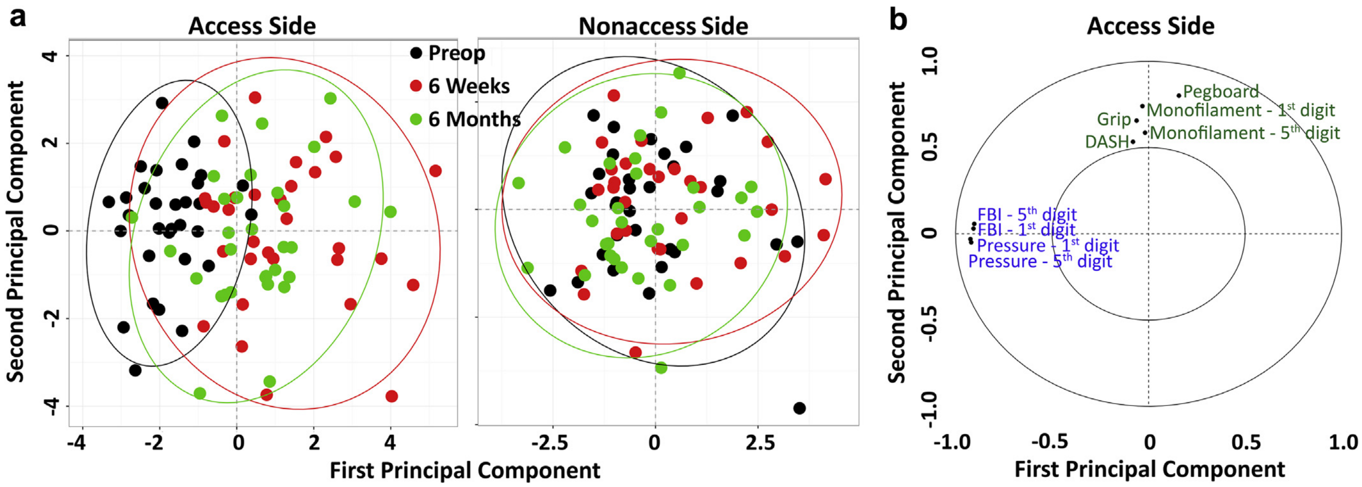

Figure 5. Principal component analysis of hemodynamic and biomechanical measures. (a) Moderate clustering of scores by time point along the first principal component reflects the significant and nearly uniform temporal changes in all hemodynamic parameters on the access-side limb. Nonaccess-side scores fail to exhibit time-dependent clustering because of the much less dramatic perturbations in nonaccess limb hemodynamics. (b) All access-side hemodynamic measurements contributed substantially to the first principal component (and thus account for the majority of the variability within the data set), yet contribute very little to the second principal component. Biomechanical tests demonstrate the converse pattern of component contribution. Such orthogonality indicates that the variation among hemodynamic measures tends to be quite different from the variation seen among biomechanical measures. The very tight clustering of hemodynamic variables reflects their nearly uniform time-dependent changes, whereas the looser clustering of the biomechanical tests underscores the differential post-operative perturbations seen among the biomechanical variables.

Associations Among Hemodynamic, Biomechanical, and Nerve Conduction Changes

We observed a common pattern in the first PCs (PC1) of biomechanical parameters (BM1), hemodynamic parameters (HD1), and nerve conduction parameters (NC1). For each parameter set, all of the individual parameters were moderately or strongly correlated with respective PC1s. For biomechanical, hemodynamic, and nerve conduction parameters, the mean absolute correlation with PC1 was 0.67 (range 0.50−0.77), 0.93 (range 0.91−0.94), and 0.75 (range 0.54−0.91), respectively. This indicates moderate to strong tracking of all parameters with each other within each parameter set. PCA of BM1, HD1, and NC1 revealed moderately strong dependence of BM1 and NC1 on each other (correlations of BM1, HD1, and NC1 with PC1 were 0.87, −0.15, and −0.90 respectively) and strong independence of HD1 relative to BM1 and NC1 (correlations of BM1, HD1, and NC1 with PC2 were −0.25, −0.98, and −0.08) respectively) (Figure 6).

DISCUSSION

This study is the first to characterize the temporal variation in both limb hemodynamics and biomechanics following AVF placement. We find that a majority of patients have significant decreases in forearm and hand pressures after surgery. A portion of the decrease in blood pressures, on both limbs, can be explained by the resumption of antihypertensive medications (which had been held immediately prior to the preoperative visit) at 6 weeks and 6 months. However, the significant pressure differences between the access and nonaccess sides reflect the direct hemodynamic effects of the AVF. Among the entire cohort, grip strength and patient perception of limb function were most affected, but no significant changes in sensation or dexterity were detected. Although the hemodynamics partially improved by 6 months postoperatively, grip strength and DASH score did not recover. Because even apparently minor changes in limb function may have a significant impact on a patient's quality of life,[19–21] the clinical problem of post-AVF hand dysfunction is prominent, and gaining insight into its biological mechanisms is essential.

Perhaps the most compelling finding was the poor association between hemodynamic perturbations and limb functional outcomes following surgery. This challenges the contemporary dogma that identifies ischemia, caused by hemodynamic alterations, as the sole cause of postoperative hand dysfunction. The observation that ischemia alone does not explain post-AVF limb dysfunction is bolstered by Hurton *et al.*, who found that although DASH scores for 123 patients receiving HD via recently created autogenous accesses were significantly worse than in age-matched controls, only 14% of the patients actually had compromised arterial perfusion pressures.[20]

We found that the various domains of hand function have varying responses to the effect of surgery. Tests that predominantly evaluate motor function, such as

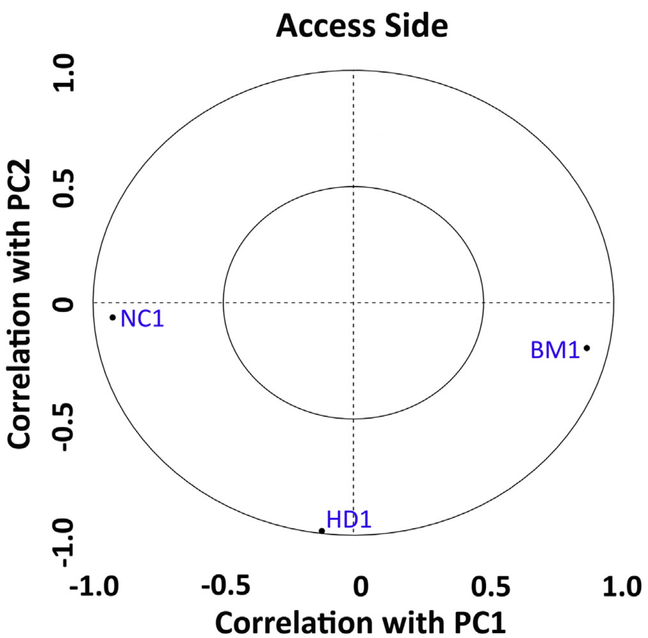

Figure 6. Principal component analysis of first principal components of biomechanical, hemodynamic, and nerve conduction parameters. Principal component analysis of the first principal components of all biomechanical parameters (BM1), all hemodynamic parameters (HD1), and all nerve conduction parameters (NC1) revealed moderately strong dependence of BM1 and NC1 on each other (correlations of BM1, HD1, and NC1 with the first principal component [PC1] were 0.87, −0.15, and −0.90, respectively) and strong independence of HD1 relative to BM1 and NC1 (correlations of BM1, HD1, and NC1 with the second principal component [PC2] were −0.25, −0.98, and −0.08, respectively). This pattern suggests that the biomechanical and nerve conduction parameters tend to track each other, yet remain relatively independent of the hemodynamic parameters.

grip strength and DASH score, demonstrated continual deterioration postoperatively, whereas digital sensation and dexterity remained essentially unaffected. This finding may reflect the different impairment thresholds among motor and sensory nerve fibers and muscle cells, or the impact of pre-existent polyneuropathy or myopathy.[8,19,20,22]

In an attempt to identify patterns of correlation among the many hemodynamic and biomechanical parameters and among patients, we used PCA. The access-side loading plot, which shows a first PC driven almost entirely by hemodynamic variables and a second PC driven largely by biomechanical variables, nicely illustrates several concepts. First, the strong contributions of all hemodynamic variables to the first PC indicate that the majority of the data set's variance lies within each of the hemodynamic variables. Second, the tight clustering of these hemodynamic variables reveals the similar manner in which these measures change. From the mixed model analysis, we can ascertain that this specifically reflects the significant time-dependent pressure changes. Third, the very limited contributions of the biomechanical tests to the first PC, in conjunction with their fairly substantial contributions to the second PC, indicates that each of the biomechanical tests tends to vary in a manner that is much different from that of the hemodynamic tests. This last point is critical because it hints at the presence of interacting mechanisms that link the initial, uniform ischemic insult to variable effects on hand function.

One such potential mechanism is a perturbation in the function of the limb's motor and/or sensory nerves in response to this new hemodynamic environment. Our nerve conduction data suggest that all measured parameters respond similarly to the effect of surgery. These nerve data tend to track the biomechanical function data over time, suggesting that the end phenotype of hand dysfunction may be partially caused by changes in nerve function. Interestingly, the hemodynamic parameters are relatively independent of both the hand function and nerve conduction parameters, suggesting that still other interacting influences (e.g., inflammation) may play roles in the causal pathway that begins with AVF surgery and ends with hand dysfunction.

Because key operative and patient-related factors, including access configuration, hand dominance, preoperative HD status, and diabetes status, could conceivably affect postoperative hand function, we included these 4 variables in our model. The altered physiology unique to the end-stage renal disease patient may contribute to hand dysfunction; global deficits in skeletal muscle function, including marked alterations in muscle bulk, strength, and activity endurance, even when compared against similarly matched patients not on HD, have been described previously.[19] Hence, we hypothesized that patients already on HD at the time of operation might show patterns of limb function different from those of patients undergoing pre-emptive AVF placement.

We found that limb dexterity differed considerably between patients who were and those who were not on preoperative HD. These differences in hand function cannot be explained by the presence of confounding factors that could correlate with the need for HD prior to surgery, such as increased age or more substantial comorbidities; a means comparison found no significant differences in these variables between the 2 groups. Instead, these functional differences may result, at least in part, from the greater degree of pre-existent muscle and nerve dysfunction caused by sequelae of renal failure itself.[19,23,24]

Hand dominance in relation to access side had significant effects on grip, pegboard performance, and thumb sensation, but these findings were not easily explainable mechanistically. A combination of small sample size and patient hand function heterogeneity may have contributed to these results. The finding that diabetic patients performed worse than their nondiabetic counterparts on all biomechanical tests is not surprising; however, interestingly, we did not identify any differences in the trajectory of limb function following surgery between these 2 patient cohorts. This suggests that diabetic patients' limbs do not necessarily suffer from an impaired ability to adapt to the postoperative environment (as might be expected) any more than the limbs of nondiabetic patients (Table S3).

Because the decision to offer surgical remediation to relieve suspected access-related hand dysfunction may be based in part on patient symptoms, we explored the correlations between patient-reported perception of hand function and objectively measured hand function. The association between a patient's report of "weakness in the arm, shoulder or hand" and measured grip force, although nonexistent preoperatively, increased postoperatively. This suggests that a patient requires some difference in grip strength (either a change over time within the same hand or a difference between hands at a given time point) to accurately gauge the degree of relative hand weakness. In contrast, monofilament test results failed to correlate significantly in any clear pattern with the patient's report of "tingling or numbness (pins and needles) in your arm, shoulder, or hand." Therefore, patient-reported symptoms may not be entirely reliable markers of actual hand dysfunction.

Our study has several limitations including the lack of a concurrently enrolled, age-matched control group (which is impossible to create because, clearly, an AVF cannot be placed in a patient without medical need). Despite this limitation, each patient had an internal control from his or her contralateral arm, and each patient had baseline preoperative testing values for reference.

Correlating our results with the Society of Vascular Surgery grading scheme for clinically significant hand ischemia, we found that a significant number of patients reported symptoms that would classify them as having Grade 1 ischemia.[25] Because a patient's report of hand symptoms such as numbness, tingling, or weakness is generally sufficient for a clinical diagnosis of ischemia following access placement, the current grading scheme and clinical guidelines may be compromised tools for identifying patients who are expected to have improved function following surgical restoration of limb perfusion.

In prospective clinical studies involving highly comorbid patient populations, such as the current study, sporadic data missingness can reduce the statistical power of the observations. However, to minimize this influence, we used modeling and statistical techniques that appropriately accounted for these discontinuities.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Form S1. Disability of Arm, Shoulder and Hand (DASH) questionnaire.

Figure S1. Effect of arteriovenous fistula (AVF) side in relation to hand dominance on biomechanical function. Grip strength, Purdue Pegboard performance, and thumb sensation were all significantly different between these 2 patient cohorts with respect to limb side (dominance* side effect, $P = 0.004$, 0.0009 and 0.04, respectively). However, the biomechanical processes driving these findings (if any), are not clear.

Figure S2. Principal component analysis of all access side hemodynamic and biomechanical variables between patient subgroups. (A, B, C) Scores plots fail to show any spatial separation between patient subgroups when partitioned by 3 of the 4 factors (arteriovenous fistula [AVF] configuration, preoperative hemodialysis (HD) status, or AVF side in relation to hand dominance). This succinctly demonstrates the lack of any consistent differences among either the hemodynamic or biomechanical variables between the subgroups within each plot. (d) However, when patients were categorized by diabetes status, moderate spatial separation is seen along the second principal component. This reflects diabetic patients' consistently worse performance on all biomechanical tests compared with the nondiabetic cohort.

Table S1. Least-squares mean biomechanical test measurements. Both access-side grip strength and Disability of Arm, Shoulder and Hand (DASH) score demonstrated progressive postoperative worsening. None of the other tests changed substantially over time or differed between sides.

Table S2. Least-squares mean limb arterial pressure and brachial pressure index measurements. Access-side pressures at all 3 anatomic locations demonstrated a substantial drop at 6 weeks followed by very modest partial recovery at 6 months. In comparison, a much smaller decrease in pressure at 6 weeks was seen throughout the nonaccess limbs. The patterns of temporal changes of the brachial pressure indices were essentially identical to those of the raw pressure measurements.

Table S3. *P* values derived from the mixed model for each variable/effect combination. Access side, time, and the interaction of side*time emerged as significant effects for nearly all hemodynamic variables. No clear pattern of significance arose from the remainder of the effects tested.

Supplementary material is linked to the online version of the paper at http://www.kireports.org.

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