Screening for Subclinical Stenosis in Native Vessel Arteriovenous Fistulae

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Abstract. Guidelines recommend the use of ultrasound dilution techniques (UDT), including measurement of access recirculation (AR) and access blood flow (Q_a), to screen for subclinical vascular access dysfunction. Although these techniques are efficacious in polytetrafluoroethylene grafts, data in native vessel arteriovenous fistulae (AVF) are lacking. A prospective observational study was conducted to evaluate the utility of UDT screening in AVF. Q_a and AR were measured bimonthly. Positive studies required fistulograms and were defined by $Q_a < 500$ ml/min, $\Delta Q_a > 20\%$ from baseline or AR $> 5\%$. Accesses with stenosis underwent percutaneous angioplasty. After 1 yr, there were 1355 mo of follow-up in 177 patients. There were 44 positive studies in 40 patients. Q_a was <500 ml/min in 36 (82%), ΔQ_a was $>20\%$ in 5 (11%), and AR was $>5\%$ in 6 (14%). Of patients with $Q_a < 500$ ml/min, 29 (81%) had stenosis. Only two patients (40%) with $\Delta Q_a > 20\%$ but $Q_a > 500$ ml/min had stenosis. No patient with AR $> 5\%$ had stenosis unless Q_a was also <500 ml/min. Immediate patency rate was 93% post-PTA. Mean Q_a increased from 303 ± 154 ml/min to 602 ± 220 ml/min ($P < 0.0001$), and mean urea reduction ratio increased from $70.4 \pm 8.4\%$ to $74.6 \pm 6.5\%$ ($P = 0.003$) post-PTA. The results demonstrate that UDT could detect subclinical stenoses in AVF, and most lesions were amenable to angioplasty. AVF that underwent PTA delivered higher Q_a and urea reduction ratio, and immediate patency rates were acceptable. Access failure after negative UDT was unusual. Measuring AR increases the time required to perform UDT but does not improve utility. Serial measurements of Q_a alone may be the best strategy for screening AVF.

Vascular access dysfunction is a major cause of morbidity in hemodialysis patients. There has been considerable interest in screening programs to detect and correct subclinical stenosis, with a view to preventing access failure (1,2). A variety of methods for screening for subclinical access dysfunction are available. UDT have been shown to measure accurately vascular access blood flow (Q_a) and access recirculation (AR), both of which can be used to detect access dysfunction (3–5). Previous studies showed that low Q_a is predictive of both access stenosis and thrombosis, but much of this work was done with polytetrafluoroethylene grafts, which may differ substantially from native vessel fistulae (6–9). Recently published Canadian guidelines recommend regular bimonthly screening of native vessel arteriovenous fistulae (AVF), using UDT to measure both Q_a and AR. These guidelines suggest that $Q_a < 500$ ml/min or a fall in Q_a (ΔQ_a) $> 20\%$ from baseline or AR $> 5\%$ be investigated with angiography (10), which is similar to the recommendations of the National Kidney Foundation Dialysis Outcomes Quality Initiative (11). The value of implementing these recommendations is unproved.

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Evidence suggests that low Q_a and high AR both are associated with access failure. However, because AR would not be expected to occur except at very low values of Q_a (12), it is unclear whether AR is of any incremental value compared with Q_a alone. In addition, performance of UDT requires the presence of a single venous segment of at least 4 cm in length. It is not known what proportion of patients with functional fistulae meet this requirement.

There were three objectives for the current study. The first was to test the clinical utility of UDT in detecting subclinical access stenosis in patients with native vessel AVF and specifically to evaluate the performance of the published guidelines. The second was to compare the clinical utility of Q_a and AR measurements in this regard. We hypothesized that measurement of AR would not result in improved diagnostic accuracy compared with Q_a alone. The third objective was to determine the proportion of patients whose fistulae were anatomically suitable for the use of UDT.

Materials and Methods

Patient Characteristics

All prevalent chronic hemodialysis patients at the Queen Elizabeth Health Sciences Center with a functioning native vessel AVF during the study period were included. There were 185 eligible patients, which was approximately 70% of our total chronic hemodialysis population. Patient demographic information was collected by research assistants and study nurses. Incident patients were added to the study as they started dialysis; patients who died or received a transplant or whose fistula failed had follow-up censored at the time of

their event. Patients were dialyzed according to their usual prescription during the study. Blood pump speeds (Q_b) were set as high as venous pressures would allow, and fistulae were cannulated with 15-gauge needles whenever possible. Urea reduction ratio (URR) is calculated monthly in our unit using standard techniques. Kt/V_{urea} is not routinely calculated.

Study Design

This was a prospective observational cohort study. We began screening patients with functioning native vessel fistulae in October 1999 as per published guidelines. Screening studies were performed bimonthly with a Transonic HD01 monitor (Ithaca, NY) using indicator dilution technology whereby the ultrasound velocity through blood is the indicator and dilution is provided by the bolus of normal saline. The validation of this device has been described elsewhere (3,5). All studies were performed by a dedicated team of nurses as part of routine clinical care; the results were reviewed by a vascular access team composed of nephrologists and dialysis nurses. Each patient had Q_a measured twice in succession during the same dialysis treatment, and the average value was recorded. AR was measured once and repeated if the first value was not 0. All measurements of AR were performed using the Transonic device rather than urea recirculation. Studies were not performed during the last hour of hemodialysis or during periods of clinically significant hypotension (at the discretion of the dialysis unit nurses).

The value of Q_a indicating that angiography was required (the "threshold value") was set at 500 ml/min as per published guidelines (10). A fall of Q_a in excess of 20% from baseline ($\Delta Q_a > 20\%$) and the presence of AR $> 5\%$ also were indications to perform angiography. The attending nephrologist was not routinely notified of the results of UDT studies; angiography was ordered by the vascular access team when the specified criteria were met. Patients for whom the attending nephrologist had ordered a fistulogram because of clinically suspected access dysfunction (*i.e.*, for any reason except for UDT data) were excluded, as the focus of this analysis was on cases of subclinical stenosis detected only by screening.

Fistula stenosis was defined by a >50% reduction in vessel diameter (11) as reported by the attending radiologist. Successful angioplasty was defined as an increase in vessel diameter postprocedure (as reported by the radiologist) in a fistula that could be used for dialysis. Patency was defined as suitability for clinical use; secondary patency included fistulae that had required multiple percutaneous interventions. Immediate and secondary patency were defined as per published guidelines (13). Follow-up continued for 12 mo after the implementation of the screening program. Pre- and postprocedure values for Q_a and URR were defined by the routine measurements immediately preceding and following the intervention. Because routine studies were performed bimonthly, the interval between measurement of these parameters and performance of angioplasty was never more than 2 mo and often was substantially shorter.

Statistical Analyses

Positive predictive value (PPV) and negative predictive value (NPV) were calculated using standard formulas. Paired two-sided *t* tests were performed on pre- and postprocedure values for Q_a and URR. The sample correlation coefficient (r) was calculated for pairs of Q_a measurements as an index of reproducibility within a given treatment. The level of statistical significance was set at $P = 0.05$. Results are expressed as mean ± SD or as percentages. Statistical analysis was performed using the Statistica software package (Statsoft Inc., Tulsa, OK).

Results

Eight of 185 patients (4.3%) did not have a venous segment of sufficient length to be studied and were excluded from further analysis. There were 1355 patient-months of follow-up in the 177 remaining patients. Mean patient age was 65.9 ± 14.9 yr, and 51.1% were male. A history of diabetes mellitus was present in 40.0%, and 53.4% had a history of vascular disease.

Analysis of the first 100 paired measurements of Q_a showed a high degree of reproducibility within a given dialysis treatment ($r = 0.98$, $P < 0.0001$). Using the definitions above, there were 44 positive studies in 40 patients (22.6% of the cohort). Q_a was <500 ml/min in 36 (82%), ΔQ_a was >20% in 5 (11%), and AR was >5% in 6 (14%). Some patients had a positive study by more than one criterion.

A positive study led to a change of needle placement in one patient; subsequent studies with needle position optimized showed greatly improved Q_a, and angiography was not performed. The remaining 43 positive studies were investigated by angiography, and 31 (72%) were found to have angiographically significant stenoses. There were 22 stenoses (71%) within 2 cm of the anastomosis, 12 peripheral stenoses (39%) that were >2 cm distal to the anastomosis, and 3 central stenoses (10%) detected. Some patients had more than one site of stenosis.

Twenty-five of 31 patients (81%) with stenosis had a successful fistuloplasty. One patient with stenosis died, and three other fistulae with stenosis failed before angioplasty could be performed (mean Q_a, 250 ± 35 ml/min; all were <300 ml/min). In the remaining two accesses, angioplasty was unsuccessful; one of these patients required insertion of a temporary dialysis catheter as the fistula was no longer usable. The other access continued to be used for dialysis, but neither the calibre of the vessel nor Q_a improved postprocedure. Four of the 25 patients required additional interventions to maintain fistula patency. The secondary patency rate for the 27 patients in whom fistuloplasty was attempted was 78.6% at 6 mo. No fistula was lost during diagnostic angiography. Defining successful angioplasty in terms of an increase in Q_a rather than by angiographic appearance did not significantly change our results, as 23 of 25 patients with an increased fistula diameter on angiography also had increased Q_a postprocedure.

Excluding the patient whose access failed postprocedure, mean Q_a increased from 303 ± 154 ml/min preangioplasty to 602 ± 220 ml/min postangioplasty ($P < 0.0001$). Mean URR also increased from 70.4 ± 8.4% preprocedure to 74.6 ± 6.5% postprocedure ($P = 0.003$). There were no changes in dialysis prescription postprocedure, and mean Q_b was not recorded.

Of patients with $Q_a < 500$ ml/min, 29 of 36 (81%) had stenosis on angiogram, and 24 (83%) had successful angioplasty. Only two of five patients (40%) with ΔQ_a of >20% (but in whom $Q_a > 500$ ml/min) had stenosis on angiography; both lesions were amenable to angioplasty. Neither of two patients with AR $> 5\%$ and $Q_a > 500$ ml/min had stenosis, but four of four with AR $> 5\%$ and $Q_a < 500$ ml/min had stenoses amenable to angioplasty. No patient had AR <5% but >0%.

In three patients, Q_a could not be measured despite a single venous segment and AR = 0%. All three underwent angiography and were found to have stenoses amenable to fistuloplasty.

Twelve patients had positive screening studies but negative angiograms. Seven such patients had $Q_a < 500$ ml/min. Two of these had needle placement optimized once their anatomy was clarified, with subsequent improvement in Q_a. Three other patients had small-calibre vessels rather than stenosis, and in the remaining two patients, no explanation for the false-positive screening study could be identified. Two patients with negative angiograms had AR > 5% and $Q_a > 500$ ml/min; one had needling optimized after angiography, with resolution of AR, and in the other, no explanation was found (AR was never detected subsequently in the access). Three patients with negative angiography had $Q_a > 500$ ml/min, no AR, and $\Delta Q_a >$ 20%. We could not detect a cause for the fall in Q_a observed in these patients, and subsequent Q_a measurements were stable or improved.

Sensitivity, specificity, and true NPV could not be calculated, because not all fistulae underwent angiography. However, among the 109 accesses in which UDT were negative during the first 6 mo of the study, only 2 subsequently failed during the follow-up period. Mean duration of follow-up in these 109 fistulae was 9.7 mo. Therefore, the NPV of UDT for access failure in this setting is approximately 98% (107 of 109) at 10 mo.

The sensitivity and specificity of UDT for stenosis can be estimated by assuming that all fistulae that had negative UDT and did not fail during the study period would have had negative angiograms. On this basis, the three criteria for positive UDT had a combined sensitivity of 94% (31 of 33) and combined specificity of 92% (135 of 147). Given the study design, it was not meaningful to perform receiver operating curve analysis to find the Q_a with optimal sensitivity and specificity for stenosis. As shown in Table 1, lowering the Q_a threshold at which angiography was performed would have improved PPV. However, it is unclear what effect (if any) this would have had on NPV.

Discussion

To our knowledge, this is the largest study of native vessel AVF that has been conducted. This prospective study shows that UDT are useful for the detection of subclinical stenosis in native vessel AVF. Twenty-seven of 177 patients studied were found to have lesions that were potentially amenable to angioplasty; mean Q_a and dialysis delivery were significantly improved after intervention. Furthermore, immediate and secondary patency rates after angioplasty were acceptable as compared with published recommendations (11) and case series (14, 15). Despite the variable anatomy of native vessel AVF, most (96%) accesses had a single venous segment of sufficient length to be studied.

Table 1. Changes in PPV with varying threshold values of Q_a[a]

Threshold Value	Positive Studies	PPV
<500 ml/min	29/36	81%
<400 ml/min	23/26	88%
<300 ml/min	14/15	93%
<200 ml/min	7/7	100%

[a] PPV, positive predictive value; Q_a, access blood flow.

We found that $Q_a < 500$ ml/min has a high PPV for stenosis, which is similar to other work done in native vessel fistulae (6). Diagnostic performance was not improved by measuring AR, which is not surprising because significant AR would not be expected when Q_a is >500 ml/min (12,16). In addition, several patients did not have detectable AR despite very low Q_a. In all cases, this occurred in association with an intra-access stenosis (between the needles used to cannulate the fistula), which explains the absence of detectable recirculation. Thus, AR does not occur until Q_a is significantly reduced and is not acceptably sensitive even at very low Q_a. In addition, measuring AR as well as Q_a significantly increases the time required to perform UDT. Because the labor costs of UDT may be reduced if they can be performed more quickly, we suggest that only Q_a be used to screen for subclinical access dysfunction in AVF.

A threshold value of $Q_a < 500$ ml/min was used in our study, as recommended by published guidelines. All three accesses that failed before fistuloplasty could be performed had $Q_a < 300$ ml/min. Because PPV increases with reductions in the threshold value for Q_a, it is possible that a threshold value of 400 ml/min might allow increased PPV without unduly sacrificing NPV. Our data are insufficient to make such a recommendation, and this issue deserves further study.

Seven of 36 patients (19%) had $Q_a < 500$ ml/min but no stenosis on angiogram. In most cases, this was due to needling technique or small native vessels. Other theoretical explanations for this phenomenon include congestive heart failure, arterial insufficiency in the ipsilateral extremity, operator error, or technical measurement error. We were not able to implicate conclusively any of these factors in our patients.

In our study, the ΔQ_a parameter was associated with a lower PPV than Q_a alone. Because Q_a may vary up to 10% within a single treatment (17), a difference of 20% between screening studies may be insufficiently specific for stenosis. We did not perform UDT during the last hour of dialysis treatments or during hypotensive episodes, which are associated with increased variability in Q_a. Although others found that decrements in Q_a were strongly associated with access failure (18,19), the great majority of accesses studied were polytetrafluoroethylene grafts, and the applicability of this finding to AVF is unclear.

No screening for subclinical access dysfunction was performed in our unit before this study. This may have resulted in a larger proportion of severe stenoses among the detected cases, which would be expected to improve the PPV of Q_a compared with ΔQ_a. Therefore, further work should be done to determine the role of ΔQ_a, including determination of the value with optimal diagnostic properties.

Because our study was uncontrolled, we are unable to assess the impact of screening on fistula survival. Although an im-

provement in Q_a and in the degree of stenosis was demonstrated in most patients who underwent angiography, we did not perform follow-up angiograms to rule out recurrent stenosis or vessel recoil. It is of note that 3 of 31 accesses that were found to have stenosis failed before angioplasty could be performed, suggesting that the likelihood of access thrombosis in patients with $Q_a < 500$ ml/min is high. This is in agreement with the available literature, including a previous cohort of native vessel fistulae (6–9,20).

Low Q_a may be a clue to improper needle placement in the absence of access stenosis. In our cohort, 3 of 12 "false positive" studies were due to difficulties with needling of the fistula, which resolved once the problem was identified, permitting higher Q_a. In addition, the inability to measure Q_a (persistence of the "unusual curve" error message) despite correct technique and a single venous segment was strongly associated with stenosis. In one case, there was an intra-access stenosis (between the dialysis needles), and in another, extensive development of collateral vessels was apparent on angiography. Thus, the inability to measure Q_a in this situation may be due to flow of the saline bolus through a collateral vessel, without ever being detected by the second ultrasound probe. Regardless of the mechanism responsible for this finding, nephrologists should consider arranging fistulography in this situation. For purposes of this analysis, we did not consider patients without measurable Q_a as cases detected by screening, because they did not meet our *a priori* definition of a positive study.

We found improved dialysis delivery after percutaneous intervention, despite that access dysfunction was not clinically suspected in these patients. Because dialysis prescription did not change and AR was evident in only a minority of patients, presumably the fistulae were able to deliver higher Q_b after successful angioplasty. Unfortunately, we did not record Q_b to confirm this hypothesis. Other workers noted an association between low Q_a and dialysis delivery but did not remeasure solute clearance after intervention (6).

Both Canadian (10) and American (11) guidelines recommend routine screening of native vessel AVF, with percutaneous or surgical correction if stenoses are found. There is no evidence that this strategy will extend fistula survival. However, this study shows that subclinical stenoses in AVF can be detected and percutaneously corrected, with acceptable immediate and secondary patency rates. In comparison, the high failure rates of stenosed fistulae that do not undergo angioplasty (6,8) suggest but do not prove that screening is beneficial.

Limitations of our study include the lack of a control group and our inability to calculate sensitivity and specificity for these techniques. In addition, our results may not apply to units that currently screen for access dysfunction using other methods such as static or dynamic pressure monitoring or Doppler ultrasound. Finally, we were not able to determine the optimal frequency of screening, because all patients were studied every 2 mo.

In summary, UDT are useful for detecting subclinical stenoses in native vessel AVF, and the majority of these accesses are anatomically suitable for study. Correcting the stenoses detected by UDT screening permitted higher Q_a and improved dialysis delivery. Performing angiography when Q_a was <500 ml/min or could not be measured was associated with a high PPV, although the ideal threshold value for Q_a remains unknown. Because measuring AR did not improve utility and is time consuming, we suggest that AR not be used routinely to screen for access dysfunction in native vessel AVF. Additional work should be done to confirm the diagnostic importance of decrements in Q_a and the optimal screening frequency in this population.

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