Diagnostic Accuracy of Ultrasound Dilution Access Blood Flow Measurement in Detecting Stenosis and Predicting Thrombosis in Native Forearm Arteriovenous Fistulae for Hemodialysis

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● *Background:* Vascular access surveillance by ultrasound dilution blood flow rate (Qa) measurement is widely recommended; however, optimal criteria for detecting stenosis and predicting thrombosis in arteriovenous fistulae (AVFs) are still not clearly defined. *Methods:* In a blinded trial, we evaluated the accuracy of single Qa measurement, Qa adjusted for mean arterial pressure (Qa/MAP), and decrease in Qa over time (dQa) in detecting stenosis and predicting thrombosis in an unselected population of 120 hemodialysis subjects with native forearm AVFs (91 AVFs, located at the wrist; 29 AVFs, located at the midforearm). All AVFs underwent fistulography, which identified greater than 50% stenosis in 54 cases. *Results:* Receiver operating characteristic curve analysis showed that dQa, Qa, and Qa/MAP have a high stenosis discriminative ability with similar areas under the curve (AUCs), ie, 0.961 ± 0.025, 0.946 ± 0.021, and 0.912 ± 0.032, respectively. In the population as a whole, optimal thresholds for stenosis were Qa less than 750 mL/min alone and in combination with dQa greater than 25% (efficiency, 90%); however, the best threshold depended on anastomotic site; it was Qa less than 750 mL/min for an AVF at the wrist and Qa less than 1,000 mL/min for an AVF in the midforearm. Qa was the best predictor of incipient thrombosis (AUC, 0.981 ± 0.013) with an optimal threshold at less than 300 mL/min (efficiency, 94%). Pooled intra-assay and interassay variation coefficients were 8.2% for MAP, 7.9% for Qa, and 11.2% for Qa/MAP. *Conclusion:* Our study shows that ultrasound dilution Qa measurement is a reproducible and highly accurate tool for detecting stenosis and predicting thrombosis in forearm AVFs. Neither Qa/MAP nor dQa improve the diagnostic performance of Qa alone, although its combination with dQa increases the test's sensitivity for stenosis. *Am J Kidney Dis* 42:331-341.
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NATIVE FOREARM arteriovenous fistulae (AVFs) are regarded as the first-choice vascular access for hemodialysis because of their superior patency rates and easier maintenance after they have fully matured.[1] However, even mature AVFs are prone to dysfunction and failure, almost invariably caused by the onset of stenosis. A number of studies have reported that prophylactic stenosis correction prolongs the useful life of the access, and routine surveillance for the detection of hemodynamically significant stenosis consequently has been recommended widely to allow preemptive intervention before thrombosis.[1]

Because the physiological effect of stenosis is to decrease access blood flow rate (Qa), direct access blood flow measurements are considered the most useful surveillance method, and ultrasound dilution[2] has became the most popular and validated technique. A major problem of Qa surveillance lies in its variability as a result of major hemodynamic changes often observed during and between dialysis sessions, making it difficult to determine accurate cutoff values for predicting access dysfunction and stenosis. In an

attempt to improve reproducibility, adjusting for mean arterial pressure (MAP; Qa/MAP or MAP/Qa, ie, access resistance)[3-5] and percentage of decrease in Qa over time (dQa),[6] rather than considering single Qa measurements, and measuring Qa early in dialysis or always at the same time[7] have been recommended for monitoring purposes.

Most experience of Qa monitoring has been gained in grafts, and criteria for detecting dys-

function are less well established in AVFs, although the current opinion is that AVFs should be monitored as outlined for grafts.[1] However, few studies have addressed the issue of the ability of Qa measurement to detect stenosis in AVFs.[8-10] Two studies proposed a Qa cutoff value less than 500 mL/min for diagnosing stenosis based on predictive values of a positive test of 56%[8] and 81%[9]; however, lack of a control group with angiographic access evaluation makes it impossible to truly evaluate predictive accuracy (ie, to identify optimal sensitivity and specificity). Another study that included grafts and a small sample of AVFs, mostly at the elbow, showed that criteria proposed by the National Kidney Foundation-Dialysis Outcomes Quality Initiative (K/DOQI) guidelines for referral for fistulography (Qa < 600 mL/min or Qa < 1,000 mL/min with >25% decrease during 4 months) ensured total sensitivity and 83% specificity for stenosis.[10] Unfortunately, results were reported without distinguishing between AVFs and grafts. Thus, applicability of these criteria to AVFs alone is questionable. The investigators reported that trend in Qa was a better predictor than absolute Qa, a finding not confirmed by others,[9] who favored single Qa measurements over dQa in a series of mostly forearm AVFs. To our knowledge, whether adjusting Qa for MAP improves stenosis prediction in AVFs is unknown.

It also has been suggested that as an alternative to Qa, measuring access recirculation is of potential benefit as a marker of stenosis in AVFs because fistulae may still be patent at lower Qas than the prescribed dialysis blood pump flow rates (Qbs).[1]

Low Qa also has been associated with increased risk for thrombosis and failure in AVFs, and various criteria have been proposed for predicting incipient thrombosis, including single Qa values ranging from less than 800 mL/min[11-13] to less than 300 mL/min[14] or dQa greater than 20%.[6] Results of most of these studies are difficult to interpret and reconcile, either because of inadequate sample sizes[6,12,15] or because they report cumulative data for both AVFs and grafts.[6,11,12,15,16] However, even studies adequate in sample size[13,17] and considering AVFs alone[13,14,17] fail to provide more consistent data, reporting threshold Qa values ranging from less

than 300 to 400 mL/min[14,17] to less than 800 mL/min.[13]

The presence of anatomic stenosis detected by duplex ultrasound or angiography reportedly is more effective or at least as effective[18,19] as Qa surveillance in predicting graft thrombosis and/or failure, but this is unlikely to apply to AVFs because they can remain patent for a long time, even at low Qas, which are usually the functional outcome of stenosis. However, a comprehensive analysis of the relationship between Qa, stenosis, and thrombosis is lacking in AVFs and is essential to the determination of an optimal access monitoring protocol.

The primary aim of our study is to evaluate the diagnostic role of Qa measurement by ultrasound dilution in detecting stenosis and predicting incipient thrombosis in native mature forearm AVFs in an unselected population of hemodialysis subjects and to identify the best thresholds. Additional aims are to evaluate Qa measurement reproducibility and compare its predictive ability with surrogate Qa markers, such as measuring access recirculation and monitoring dialysis Qb.

PATIENTS AND METHODS

This blinded study was performed in an unselected population of hemodialysis subjects from 2 hemodialysis units at the Ospedale Policlinico (unit A) and Ospedale Civile Maggiore (unit B) in Verona, Italy, between February 1998 and December 2001.

All subjects gave their informed consent to the study protocol, which was approved by the local ethical committee.

Study Design

Prediction of stenosis. One hundred twenty-seven prevalent hemodialysis subjects with native, mature, forearm, radiocephalic AVFs were evaluated.

In February to April 1998, a total of 46 prevalent subjects were enrolled from unit A. In January to May 2001, an additional 45 eligible subjects from unit A and 36 subjects from unit B were added to the study.

In the vast majority of subjects, the arteriovenous anastomosis was located at the wrist, but in 29 subjects, it was located in the midportion of the forearm, up to approximately 8 cm below the crease of the elbow either because of a more distal AVF failing to mature (n = 8) or electively (because suitable distal arteries and superficial veins were lacking as a consequence of arterial wall thickening caused by atherosclerosis and/or calcification and repeated venipuncture), according to the surgical team's clinical judgment.

All AVFs were evaluated by Qb monitoring, Qa measurement by ultrasound dilution, and access recirculation measured by urea-based (Ru) and ultrasound dilution (Rhd) methods.

Tests under investigation and reference standard were evaluated separately; the former were performed 1 to 3 weeks before fistulography. The presence of significant stenosis ($>50\%$ reduction in vessel diameter compared with the adjacent segment) was ascertained and quantified by 1 of the 2 attending radiologists, who were unaware of results of index tests; therefore, our study can be considered blinded. The angiogram usually was assessed by only 1 radiologist.

Qa measurements were unobtainable in 4 of 127 subjects (shown on the Transonic [Transonic System Inc, Ithaca, NY] device as an unusual curve); thus, these AVFs were not included in the final analysis. Fistulography showed they all had early venous collaterals immediately beyond the anastomosis, an anatomic condition that makes it impossible to cannulate the main trunk of the access and leads to arterial and venous needles being placed in 2 different noncommunicating branches, making flow measurement impossible because of lack of recirculation of the saline bolus with inverted blood tubing. Three AVFs had a normal angiogram, whereas stenosis was documented in 1 AVF. Fistulography showed a subclavian stenosis in 3 subjects, and these AVFs (Qas of 887, 1,016, and 1,176 mL/min) also were excluded from the final analysis, which therefore was limited to a cohort of 120 AVFs.

The stenosis-predicting role of changes in Qa over time was evaluated prospectively in a subpopulation of 42 AVFs. Because the aim of the study is to identify stenosis, not evaluate its rate of progression, only AVFs with no stenotic lesions on the baseline angiogram were included in this part of the study. Twenty-four of 66 eligible AVFs were lost to follow-up because of patient death ($n = 9$), kidney transplantation ($n = 5$), transfer to other facilities ($n = 6$), or refusal of a follow-up angiogram ($n = 4$); therefore, 42 nonstenotic AVFs for which at least 2 serial Qa measurements and fistulograms were available were included in the final analysis. During follow-up, Qa was monitored every 2 to 4 months, and fistulography was performed anytime a dQa greater than 15% was documented or after a median of 16.5 months (10th to 90th percentile, 11.0 to 26.0 months) from the initial angiogram in AVFs showing no significant change in Qa. Median follow-up was 12.0 months (10th to 90th percentile, 7.0 to 26.0 months). During follow-up, 20 AVFs developed greater than 50% stenosis after a median of 10.0 months (10th to 90th percentile, 5.0 to 20.0 months), whereas fistulograms showed no changes in the remaining 22 AVFs.

Prediction of thrombosis. The role of index tests and the presence of stenosis in predicting incipient (ie, within 7 months of the initial angiogram) thrombosis was evaluated prospectively in a subpopulation of 65 AVFs with an adequate intervention-free follow-up.

Fifty-five of 120 AVFs were excluded from this part of the study because either they underwent treatment of stenotic lesions ($n = 14$) or follow-up with a patent access was less than 12 months because of death ($n = 15$), kidney transplantation ($n = 6$), transfer to another facility ($n = 6$), or end of follow-up ($n = 14$).

The anastomosis was located at the wrist in 52 AVFs and midforearm in 13 AVFs. Forty-one AVFs had greater than 50% stenosis.

Serial Qa measurements were available in only 30 AVFs; thus, the predictive role of dQa for thrombosis could only be calculated in this subgroup.

Twelve AVFs thrombosed within 7 months of the angiogram after a median of 4.0 months (10th to 90th percentile, 2.0 to 7.0 months), and thrombosis rate in the population as a whole was 0.162 events/AVF-year at risk.

Reproducibility. Evaluation of reproducibility was performed April to July 1998. To minimize hemodynamic status–dependent intra-assay Qa variability, no antihypertensive medication was administered before dialysis, intradialytic fluid loss was set at a rate no greater than 800 mL/hour, and Qa measurements were performed in the first 90 minutes of hemodialysis sessions in stable cardiovascular conditions. Measurements were not performed if predialysis MAP differed considerably from the subject's customary value or MAP varied during Qa testing by more than 15 mm Hg from one measurement to another and from the predialysis value. To ensure interassay reproducibility, Qa measurements were postponed if predialysis MAP showed differences greater than 15 mm Hg with respect to previous sessions in which measurements had been performed.

These conditions were not difficult to meet because only 28 of 390 Qa measurements (7.2%) were postponed because of intradialytic cardiovascular instability, and 23 of 162 measurements (14.2%), because of predialyis MAP differences greater than 15 mm Hg in serial Qa measurements.

In addition, position of the needles, evaluated as distance from the arteriovenous anastomosis, always was recorded to place the needles in approximately the same position in subsequent measurements, and Qa measurements were performed in triplicate and by the same operators (N.T., L.G., and V.B.).

Access Surveillance

Qa was measured by means of ultrasound dilution technique using the Transonic HD01 monitor, as described elsewhere.[20] AVFs were cannulated with 15-G needles, and the arterial needle was placed in the main trunk of the feeding vein, proximal to any collateral veins and facing the incoming blood flow. The venous needle always was placed facing the shoulder, either in the main stream of the access or one of its branches.

Qa measurements were performed in triplicate within 30 to 90 minutes after starting dialysis and then averaged. Qb was set at greater than 200 mL/min, and ultrafiltration was turned off 3 minutes before taking measurements.

Arterial blood pressure was measured using an oscillometric cuff method immediately after each Qa measurement, Qa was adjusted for MAP (Qa/MAP), and measurements were then averaged.

dQa was calculated as follows:

$$\text{dQa (\%)} = -100 \times (\text{Qa2} - \text{Qa1})/\text{Qa1}$$

where Qa1 is the initial value and Qa2 is the value at the subsequent measurement, with dQa greater than 0% indicating that Qa decreased over time. Values less than 0%, indicating an increase in Qa, were reported as 0%.

Access recirculation was evaluated by means of both Rhd using the Transonic HD monitor and Ru using the slow-flow technique.[21] Tests were performed within 30 to 60 minutes

of starting the dialysis treatment. For Ru measurement, arterial (A) and venous (V) samples were draw at a Qb of 300 to 350 mL/min, and the systemic (S) sample was drawn from the arterial tubing after reducing Qb to 50 mL/min for 20 to 30 seconds. Blood urea nitrogen concentrations were measured in all samples, and Ru was calculated as follows:

$$Ru\ (\%) = (S - A)/(S - V) \times 100$$

Negative arterial prepump pressure and Qb were monitored during each dialysis session: the negative arterial pressure alarm was set at −250 mm Hg, and any persistent (ie, in at least 2 consecutive hemodialysis sessions) decrease in prescribed Qb (dQb, in milliliters per minute) that was needed to proceed with dialysis because of a high negative arterial pressure was recorded.

Fistulography

Fistulography was performed before dialysis using the arterial needle for contrast medium injection. The AVF then was visualized in its entirety, inverting flow in the venous limb with an inflated sphygmomanometer. In the few occasions in which it was impossible to visualize the anastomosis, a fistulogram was obtained by puncturing the brachial artery on a nondialysis day. Images were acquired in at least 2 planes.

Statistical Analyses

Data are reported as percentage, mean ± SD, or median (10th to 90th percentile), unless stated otherwise. Normally distributed data were analyzed by means of unpaired *t*-test; and skewed data, by Mann-Whitney *U* test.

To identify optimal test and threshold values for predicting stenosis and incipient thrombosis, receiver operating characteristic (ROC) curve analysis was performed[22] by plotting sensitivity versus false-positive rate (FPR) at different cutoff levels of the predictor being tested. Sensitivity is defined as the percentage of stenotic or thrombosed AVFs with a positive test result (true-positive [TP] result). Specificity is defined as the percentage of AVFs with no stenosis or thrombosis with a negative test result (true-negative [TN] result), and FPR (equal to 1- specificity), as the percentage of AVFs with no stenosis or thrombosis that tested positive. The diagnostic efficiency of different test thresholds is defined as the sum of TP and TN results, ie, the percentage of AVFs in which test result and diagnosis agree in the population as a whole.

Post-test probabilities after a positive (PPP) or negative test result (PPN) for stenosis and incipient thrombosis also were calculated for different thresholds of the index tests, as follows:

$$PPP\ (\%) = prevalence \times TP/(prevalence \times TP)$$
$$+ ([1 - prevalence] \times FPR)$$

$$PPN\ (\%) = prevalence \times (1 - TP)/(prevalence$$
$$\times[1 - TP]) + ([1 - prevalence] \times TN)$$

where prevalence is the percentage of AVFs with stenosis or thrombosis.

Table 1. Subject Characteristics

	Normal AVFs	Stenotic AVFs	P
No. of subjects	66	54	
Age (y)	63 ± 12	61 ± 14	NS
Sex (men/women)	41/25	36/18	NS
Proportion of diabetes (%)	15.1	31.5	0.048
Proportion of cardiovascular disease (%)	36.4	42.6	NS

Abbreviation: NS, not significant.

We used the coefficient of variation (CV; CV = 100 × SD/mean) to describe intra-assay and interassay variability as a percentage of the average value. Pooled intra-assay and interassay SDs and CVs for Qa, MAP, and Qa/MAP also were calculated using equations described by De Soto et al.[23]

Significance is set at 2-sided *P* less than 0.05.

Analyses were conducted using SPSS for Windows, version 11.0 software (SPSS Inc, Chicago, IL). ROC curve analysis was performed using the Astute DDU Software (The University of Leeds, Leeds, UK).

RESULTS

Characteristics of subjects and AVFs considered in the final analysis are listed in Tables 1 and 2.

In this unselected group of subjects with forearm AVFs, the prevalence of stenosis was 45.0% and was similar in both wrist (43 of 91 AVFs; 47.2%) and midforearm AVFs (11 of 29 AVFs; 37.9%). Subjects with stenosis did not differ from those with normal AVFs in terms of age, sex distribution, or prevalence of symptomatic cardiovascular disease, but they had a greater prevalence of diabetes.

Stenotic AVFs had a significantly greater prevalence of access recirculation and dQb.

Qa values are shown in Fig 1. Median Qa was 1,024 mL/min (10th to 90th percentile, 602 to 1,362 mL/min) in normal wrist AVFs, 387 mL/min (10th to 90th percentile, 137 to 694 mL/min) in stenotic wrist AVFs, 1,496 mL/min (10th to 90th percentile, 1,016 to 2,390 mL/min) in midforearm normal AVFs, and 573 mL/min (10th to 90th percentile, 310 to 879 mL/min) in stenotic midforearm AVFs. Stenotic AVFs had significantly lower median Qa values than normal AVFs in both the wrist (*P* < 0.001) and midforearm (*P* < 0.001) groups. Qa levels were significantly greater in midforearm than wrist AVFs in both normal (*P* < 0.001) and stenotic accesses (*P* = 0.021).
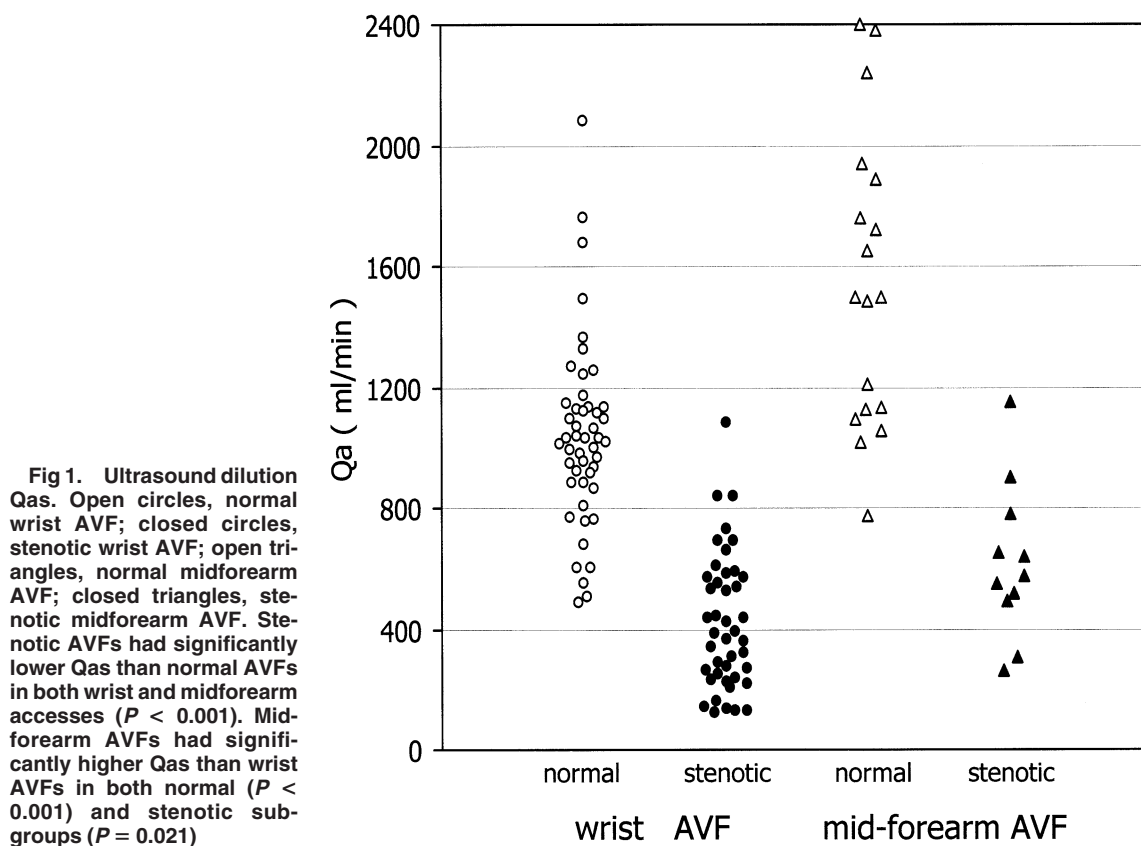
Table 2.   AVF Characteristics

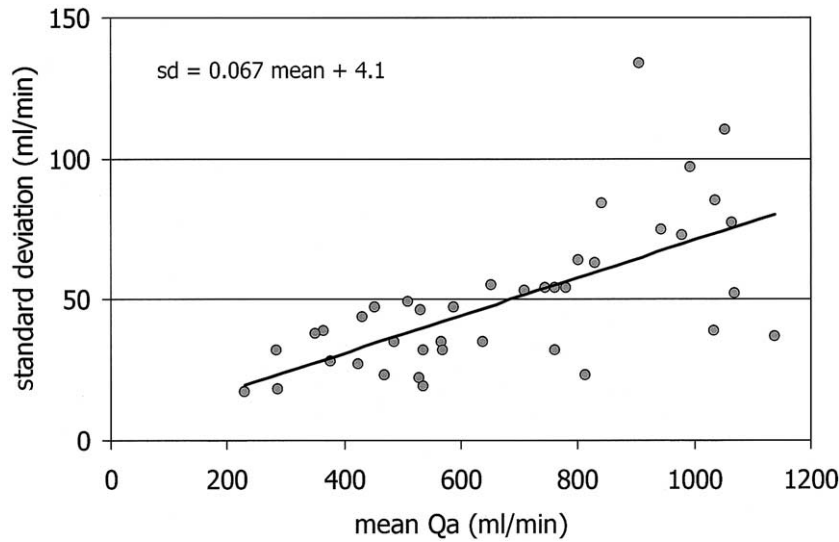|	Normal AVFs	Stenotic AVFs	P
No. of AVFs	66	54	
AVF age (mo)	11 (2–27)	12 (2–28)	NS
AVF anastomosis location (%)			
Wrist	73.9	79.6	NS
Midforearm	26.1	20.4	NS
Degree of stenosis (%)	0 (0–30)	78 (65–90)	<0.001
Proportion of multiple stenoses (%)	—	25.9	
Proportion of stenosis > 2 cm (%)	—	11.1	
Location of stenosis (%)			
Arterial	—	5.5	
Venous perianastotic (initial 4 cm)	—	81.4	
Venous distal (past initial 4 cm)	—	13.1	
Prevalence of Rhd > 0 (%)	1.5	26.9	<0.001
Decrease in Qb to continue dialysis (mL/min)	0 (0–10)	40 (23–45)	<0.001

Abbreviation: NS, not significant.

Analyses of Variability

Intra-assay CVs were 5.0% ± 2.7% for Qa, 5.3% ± 2.8% for MAP, and 6.2% ± 3.3% for Qa/MAP (n = 108). CVs for Qa and Qa/MAP differed significantly (*P* = 0.004). Interassay variability was evaluated in 40 AVFs with duplicate Qa measurements performed a median of 2.0 weeks (10th to 90th percentile, 1.0 to 7.0 weeks) apart; hemodynamic conditions at the time of testing were similar, shown by a mean

Fig 1.   Ultrasound dilution Qas. Open circles, normal wrist AVF; closed circles, stenotic wrist AVF; open triangles, normal midforearm AVF; closed triangles, stenotic midforearm AVF. Stenotic AVFs had significantly lower Qas than normal AVFs in both wrist and midforearm accesses (*P* < 0.001). Midforearm AVFs had significantly higher Qas than wrist AVFs in both normal (*P* < 0.001) and stenotic subgroups (*P* = 0.021)

Fig 2. Relationship between pooled intra-assay and interassay Qa means and SD. The 2 parameters correlated significantly (r = 0.682; P < 0.001).

predialysis MAP difference of 8.1 ± 4.2 mm Hg between the 2 sessions. Pooled intra-assay and interassay SDs and CVs were 56.5 mL/min and 7.9% for Qa, 7.85 mm Hg and 8.2% for MAP, and 0.96 mL/min/mm Hg and 11.2% for Qa/MAP, respectively. Qa measurement precision also was evaluated by plotting mean pooled intra-assay and interassay Qa values against SD, shown in Fig 2.

Diagnostic Accuracy in Detecting Stenosis

For stenosis, the diagnostic accuracy of Qa measurements is shown in Fig 3. ROC curve analysis showed that single Qa measurement, Qa/MAP, and dQa had very high discriminative ability with similar areas under the curve (AUCs).

When ROC curve analyses were performed for Qa and Qa/MAP in the group of 42 AVFs for which dQa data were available, AUCs for Qa and Qa/MAP were 0.912 ± 0.047 and 0.916 ± 0.053, respectively; neither differed significantly from those obtained in the general population.

The best combinations of sensitivity and FPR for surrogate markers of low blood flow also are shown in Fig 3. AUCs for dQb, Ru, and Rhd were 0.724 ± 0.05, 0.636 ± 0.055, and 0.629 ± 0.053, respectively; all were significantly lower than those obtained for Qa, dQa, and Qa/MAP measurements (P < 0.05).

The diagnostic accuracy of stenosis was evaluated for different thresholds of different tests; the best tests and thresholds in order of efficiency are

listed in Table 3. The most efficient predictor of stenosis was a single Qa less than 750 mL/min, either alone or in combination with dQa greater than 25%. dQa and Qa/MAP did not improve the diagnostic efficiency of the single Qa measurement, even at their most efficient values of dQa greater than 20% and Qa/MAP less than 6.5 mL/min/mm Hg.

Including the 3 subjects with subclavian stenosis in the analysis led to a slight reduction in diagnostic accuracy for stenosis. For instance,
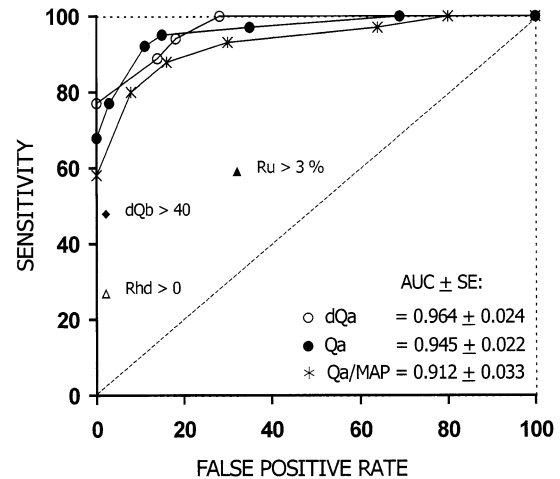
Fig 3. ROC curve analysis of Qa measurement as predictor of stenosis. Best combinations of sensitivity and FPR for Ru, Rhd, and dQb are included. Dashed line at 45° indicates no discriminative ability (AUC = 0.5).

Table 3. Diagnostic Accuracy of Different Tests and Thresholds to Detect Stenosis

	Efficiency (%)	Sensitivity (%)	Specificity (%)	PPP (%)	PPN (%)
Either Qa <750 mL/min or dQa >25%	90.4	95.0	86.3	85.2	5.2
Qa <750 mL/min	90.1	89.0	90.9	89.0	9.1
Either Qa <600 mL/min or dQa >25%	88.1	95.0	81.8	82.6	5.3
dQa > 20%	88.1	90.0	86.3	85.7	9.5
Qa < 900 mL/min	86.6	96.3	78.8	78.8	3.7
Qa < 600 mL/min	86.6	75.9	95.4	93.2	17.1
Qa/MAP < 6.5	85.5	78.5	91.6	89.2	17.0
Qa < 500 mL/min	79.1	55.5	98.4	96.7	27.0
dQb > 40 mL/min	76.0	48.0	98.4	96.1	29.7
Rhd > 0	66.6	26.9	98.4	93.3	37.3
Ru > 3%	64.2	59.1	68.3	60.4	32.8

the sensitivity of Qa less than 750 mL/min decreased from 89.0% to 84.2%, and its efficiency changed from 90.1% to 87.8%. If the 4 additional AVFs in which Qa measurements were unobtainable also are included, there was an additional decline in diagnostic accuracy, with efficiency of 85.0%, sensitivity of 82.8%, and specificity of 87.0%, values still compatible with an excellent diagnostic performance.

The best diagnostic performances of dQb, Ru, and Rhd showed efficiency values that make their clinical utility doubtful.

Because wrist and midforearm AVFs had significantly different Qa levels in both normal and stenotic accesses, we evaluated whether diagnostic criteria for stenosis should be different according to location of the anastomosis (Table 4). The most efficient value for detecting stenosis was Qa less than 750 mL/min in wrist AVFs and Qa less than 1,000 mL/min in midforearm AVFs. Adjusting Qa for MAP did not improve the diagnostic accuracy of single Qa measurements in either subgroup. The diagnostic accuracy of dQa in the 2 subgroups was not calculated given the limited number of midforearm AVFs with available data (3 normal and 3 stenotic AVFs).

Diagnostic Accuracy in Predicting Thrombosis

Figure 4 shows the diagnostic accuracy of the different tests in predicting incipient thrombosis according to ROC curve analysis. Single Qa measurement showed the greatest AUC, which was the same for Qa/MAP (AUC, 0.975 ± 0.016; data not shown in Fig 4). All the other tests were less effective, but still acceptable, discriminators. Figure 4 also shows the sensitivity and FPR of the presence of anatomic stenosis for incipient thrombosis; the AUC of 0.726 ± 0.065 was significantly lower than for Qa ($P = 0.036$).

ROC curves analyses for Qa, Qa/MAP, Ru, Rhd, dQb, and stenosis were reevaluated in the group of 30 AVFs with dQa data available: AUCs were 0.964 ± 0.029 for Qa, 0.947 ± 0.045 for Qa/MAP, 0.813 ± 0.104 for Ru, 0.702 ± 0.137 for Rhd, 0.782 ± 0.173 for dQb, and 0.711 ± 0.119 for stenosis. None of these differed significantly from those obtained in the general population.

Table 5 lists optimal tests and thresholds for predicting thrombosis in order of efficiency. The most efficient test was Qa less than 300 mL/min for both wrist and midforearm AVFs. Qa/MAP

Table 4. Diagnostic Accuracy of Qa Measurements to Detect Stenosis in Wrist and Midforearm Fistulae

	Efficiency (%)		Sensitivity (%)		Specificity (%)		PPP (%)		PPN (%)	
	dAVF	pAVF	dAVF	pAVF	dAVF	pAVF	dAVF	pAVF	dAVF	pAVF
Qa < 750 mL/min	90.1	89.6	93.0	72.7	87.5	100	86.9	100	6.7	14.3
Qa< 1,000 mL/min	84.6	93.1	97.6	90.9	72.9	94.1	76.3	90.9	2.8	5.6
Qa/MAP < 6.5	85.3	82.6	82.7	63.6	89.2	100	86.2	100	15.4	25.0
Qa/MAP < 9.5	70.6	86.9	93.1	90.9	51.3	83.3	61.7	83.3	9.6	10.0

Abbreviations: dAVF, wrist AVF; pAVF, midforearm AVF.
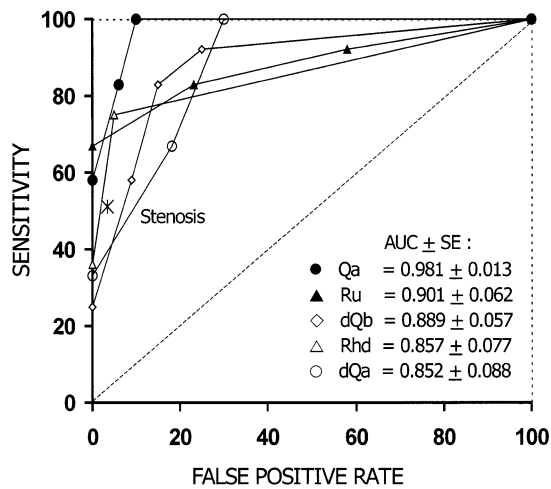
Fig 4. ROC curve analysis of Qa, dQa, Ru, Rhd, and dQb measurements as predictors of incipient thrombosis. Sensitivity and FPR values of the presence of stenosis are included. Dashed line at 45° indicates no discriminative ability (AUC = 0.5).

did not improve the diagnostic efficiency of single Qa measurement; access recirculation measurements and dQb also were good discriminators, whereas the lowest predictive accuracy was recorded for dQa and the presence of stenosis.

DISCUSSION

K/DOQI guidelines recommend routine surveillance for hemodynamically significant stenosis in both grafts and AVFs because of the evidence that prophylactic stenosis correction improves access patency rates.[1]

However, this approach has been questioned and considered premature because there still are several unresolved issues concerning the predictive accuracy of the monitoring tools; full risk, benefit, and cost accounting of the surveillance program; optimal timing of a corrective interven-

tion; and lack of studies adequate in methods to address these issues.[19]

Regarding accuracy in diagnosing stenosis in AVFs, the few available studies[8-10] have method biases, eg, small sample size,[10] combined reports on grafts and AVFs,[10] and no concurrent control group,[8,9] making accurate identification of optimal criteria for detecting stenosis impossible. Most studies on diagnostic accuracy in predicting thrombosis also have been biased by small sample size[9,12,15] and the reporting of cumulative data for AVFs and grafts,[6,11,12,15,16] and they have proposed a wide variety of diagnostic criteria. In addition, the poor reproducibility of Qa measurement[4,23] remains a source of major concern for the clinical applicability of Qa surveillance.

The pooled CV for Qa measurements and the regression equation between mean Qa values and their SDs obtained in our study indicate that assay reproducibility accounts for up to 16% of Qa measurement variability, even under standardized conditions in which hemodynamic variability is minimized. Qa variability was lower in our study than that reported for grafts,[23] but similar to what others reported in AVFs,[4] who found pooled CVs similar to ours for MAP (7.9% versus 8.2%), Qa (9.5% versus 7.9%), and MAP/Qa (11.9% versus 11.2% for Qa/MAP in our study) in hemodynamically stable subjects during the first hour of dialysis.

Despite the relatively high variability, Qa measurement shows an excellent diagnostic performance in detecting access dysfunction; this finding is explained partially by the high prevalence of stenosis and thrombosis in our unselected forearm AVF population, a situation that usually ensures good performance, even for tests with less than ideal diagnostic accuracy. ROC curve analysis showed that Qa measurement by ultra-

Table 5.   Diagnostic Accuracy of Different Tests and Thresholds to Predict Thrombosis

	Efficiency (%)	Sensitivity (%)	Specificity (%)	PPP (%)	PPN (%)
Qa < 300 mL/min	93.8	91.6	94.3	78.5	2.0
Qa < 350 mL/min	92.3	100	90.5	70.5	0
Qa/MAP < 2.5	91.4	75.0	98.0	88.8	5.7
Rhd > 2%	90.7	75.0	94.3	75.0	5.7
Ru > 5%	87.6	66.6	92.3	66.6	7.7
dQb > 60 mL/min	87.6	50.0	92.6	75.0	10.6
dQa > 25%	76.7	66.7	77.7	25.0	4.6
Stenosis	55.3	100	45.2	29.2	0

sound dilution had AUC values greater than 0.90 for detecting stenosis and predicting thrombosis, indicating that the test would be useful in clinical practice. For the diagnosis of stenosis, Qa values ranging from less than 600 mL/min to less than 900 mL/min showed an excellent combination of sensitivity and specificity, with efficiency greater than 85%.

Neither Qa/MAP nor dQa, even at their best thresholds of Qa/MAP less than 6.5 and dQa greater than 20%, improved the performance of absolute Qa measurement, as reported by others for dQa as a predictor of stenosis in AVFs[9] and dQa and Qa/MAP as predictors of thrombosis in grafts.[24,25]

Conversely, combining Qa with dQa proved capable of providing additional improvement in diagnostic accuracy. The greatest efficiency value was obtained for the either/or combination of Qa less than 750 mL/min and dQa greater than 25%, which improved sensitivity without a substantial increase in FPR compared with Qa less than 750 mL/min. The combination is preferable to single Qa measurements because recent reports showing that early identification and correction of stenosis improve AVF survival[10,26,27] favor tests with the greatest sensitivity, even at the cost of an increase in number of unnecessary diagnostic procedures.

Our results show that criteria proposed by K/DOQI guidelines for referral for angiography also are highly accurate for forearm AVFs, although a greater Qa threshold than the Qa less than 600 mL/min proposed by K/DOQI may be more appropriate. They also favor implementing surveillance programs based on regular serial Qa measurements, although the improvement in sensitivity should be weighed against the greater costs of surveillance and greater workload for the dialysis staff.

We confirm that the threshold of Qa less than 500 mL/min, recently proposed as the best criterion for detecting stenosis in AVFs,[9] has a high predictive value of a positive test, but this threshold had such low efficiency and sensitivity ratings that its clinical value is questionable because it is unable to identify a large number of AVFs that may benefit from stenosis correction. Instead, when a surveillance program based on frequent serial Qa measurements is unfeasible, a threshold of Qa less than 900 mL/min should be used as the indication for fistulography given its high sensitivity (96%) and acceptable FPR (21%).

Our study also shows that location of the arteriovenous anastomosis in forearm AVFs is an important determinant of Qa levels because both normal and stenotic midforearm AVFs had greater Qa values than wrist AVFs. This probably is the result of a greater arterial vasodilatory response to the construction of the anastomosis as a consequence of the greater arterial diameter and less pronounced atherosclerotic wall lesions and calcification of more proximal vessels.[28]

As expected, optimal Qa and Qa/MAP threshold levels for stenosis were greater in midforearm than wrist AVFs. Unfortunately, the small number of midforearm AVFs with serial Qa measurements and fistulograms made it impossible for us to compare the diagnostic role of dQa in the 2 subgroups.

That Qa/MAP should offer no advantage over Qa in terms of diagnostic accuracy for stenosis (and thrombosis) may be interpreted as suggestive of a limited role of changes in MAP on Qa levels in fistulae, but it more likely is caused by our study protocol, in which MAP variation was minimized by taking Qa measurements in the first 90 minutes of dialysis in sessions with stable cardiovascular conditions. As long as Qa measurements are performed under standardized conditions and in dialysis sessions with reproducible hemodynamic status, adjustment of Qa for MAP is not worthwhile because the increase in complexity of surveillance does not benefit diagnostic performance.

Surrogate markers of Qa, such as Qb monitoring and access recirculation measurement, offer no advantage over Qa measurement in terms of detecting stenosis and are of uncertain clinical utility because of their low sensitivity.

Qa measurement also proved to be the best marker of incipient thrombosis in AVFs. The best thresholds were between Qa less than 300 mL/min and Qa less than 350 mL/min, the former showing the best efficiency, and the latter, the best absolute sensitivity and acceptable FPR. Thresholds identified by our study are similar to those proposed by the largest published study that identified duplex ultrasound Qa less than 400 mL/min as the best predictor of thrombosis in AVFs.[17]

Measuring access recirculation also proved to

be a good predictor of incipient thrombosis in AVFs; the most efficient values were Rhd greater than 2% and Ru greater than 5%, but the lower sensitivity makes this test less useful than Qa surveillance.

The near-perfect predictive power for thrombosis shown by Qa and the excellent diagnostic performance by access recirculation should be considered with caution because our study may overestimate predictive accuracy because of the relatively small sample size, prolonged observation period, and unintentional selection bias associated with subgroup analysis. However, our data indicate that detecting Qa less than 350 mL/min and/or the presence of access recirculation should prompt for immediate action in AVFs to prevent thrombosis.

dQa proved less accurate in predicting thrombosis than single Qa measurement, supporting the notion that a decrease in flow over time better reflects a developing process, such as stenosis, whereas absolute Qa levels are related to patency in AVFs.[29] However, this part of the study may be underpowered for an accurate evaluation of the role of dQa in predicting thrombosis, and larger prospective trials obviously are needed.

Our study shows that identifying anatomic stenosis in AVFs is less effective than evaluating functional and/or hemodynamic parameters to pinpoint an access at risk for incipient failure. The presence of stenosis has a poor predictive value for future short-term episodes of thrombosis, thus confirming the observation that a stenotic AVF can remain patent for a long time,[1] but also indicating that patency depends on Qa levels being greater than a critical threshold of 300 to 350 mL/min. Our study also indicates that nonstenotic AVFs virtually never clot, confirming previous reports that stenosis almost invariably underlies a thrombotic event in AVFs.[30]

In predicting both stenosis and thrombosis, Qa showed greater AUC values than those reported for grafts,[31] suggesting that Qa measurement is better suited to predict dysfunction in AVFs than grafts. This discrepancy may be explained by the different locations of stenosis in the accesses, being largely perianastomotic (inflow) in AVFs and usually located in the draining vein (outflow) in grafts, because it has been shown that high inflow resistance has a more profound effect on total access resistance, and thus on Qa, than high outflow resistance.[32]

Our study also shows that ultrasound dilution Qa measurements are feasible in the vast majority of forearm AVFs and suggests that if Qa is unobtainable, fistulography and/or duplex ultrasound evaluation of the access is warranted. It also suggests that Qa monitoring is inaccurate in detecting subclavian stenosis, which may be identified better by other means, eg, an increase in dialysis venous pressure and/or arm swelling.

Finally, the study provides information on the optimal frequency of Qa surveillance in AVFs: the median time to develop stenosis and thrombosis observed in our prospective trial suggests that a surveillance program based on quarterly/bimonthly Qa measurement should be cost-effective in detecting AVFs at risk.

In conclusion, our study shows that ultrasound dilution Qa measurement is a sufficiently reproducible and highly accurate technique to detect stenosis and predict thrombosis in native mature forearm AVFs. For stenosis, diagnostic accuracy of single Qa measurement is not improved by adjusting for MAP or dQa, whereas combining Qa and dQa improves sensitivity, justifying surveillance programs based on serial Qa measurements. In the group of AVFs as a whole, optimal criteria for stenosis were Qa less than 750 mL/min and its either/or combination with dQa greater than 25%, the latter preferable to the former because it induces a slight increase in sensitivity. However, the optimal threshold for stenosis varies according to arteriovenous anastomosis location, being higher for the more proximal forearm AVFs (Qa $<$ 1,000 mL/min in midforearm AVFs versus Qa $<$ 750 mL/min in wrist AVFs). Single Qa measurement also proved to be a highly accurate predictor of incipient thrombosis in forearm AVFs; the ideal threshold was between less than 300 and less than 350 mL/min. Qa/MAP and dQA impaired, rather than improved, single Qa diagnostic performance, whereas access recirculation and dQb showed good predictive power for thrombosis, although they were inferior to Qa because of their lower sensitivity.

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