Comparing non-invasive diagnostic methods for arteriovenous fistula stenosis: a prospective study

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Abstract
Purpose  International guidelines recommend screening for arteriovenous fistula (AVF) stenosis using various non-invasive methods. We evaluate different non-invasive AVF flow measurements for detecting AVF stenosis.
Methods  Twenty-three haemodialysis patients with suspected AVF stenosis are enrolled based on abnormal physical signs or high venous pressure during dialysis. Ultrasound dilution, urea dilution, Doppler ultrasonography, and fistulography are performed on all patients. The accuracy of three non-invasive methods is compared.
Results  Fistulography reveals AVF stenosis in 18 patients, 12 of whom have severe stenosis (greater than 50% stenosis in diameter). Concerning the location of the stenosis lesions, eight are at the inflow site, six at the outflow site, and four on both sites. Receiver operating characteristic curve analysis shows that Doppler ultrasonography has a high discriminative ability and the averaged areas under the curves are 0.933 (95% confidence interval [CI]; 0.81 to 0.99) for stenosis and 0.929 (95% CI 0.82–0.99) for severe stenosis. The sensitivity of each method for the prediction of access stenosis using ultrasound dilution, urea dilution, and Doppler ultrasonography is 73%, 73%, and 80%, respectively. The respective specificity of each method is 40%, 80%, and 100%, respectively. Physical examination (PE) shows an 80% sensitivity and 80% specificity in the detection of AVF stenosis. The combination of Doppler ultrasound with PE produces the highest sensitivity (93%) for detecting AVF stenosis.
Conclusions  Doppler ultrasound combined with physical examination is more accurate than other non-invasive methods for detecting AVF stenosis.

Keywords  Hemodialysis · Arteriovenous fistula · Arteriovenous fistula stenosis · Access flow

Abbreviations

| Abbreviation | Description        |
|--------------|--------------------|
| AVF          | Arteriovenous fistula |
| HD           | Hemodialysis       |
| ROC          | Receiver operating characteristic |
| ESRD         | End-stage renal disease |
| Qb           | Blood flow rate    |
| BUN          | Blood urea nitrogen |
| R            | Recirculation      |
| Qa           | Access flow        |

a  Arterial
v  Venous

Background
Reliable arterio-venous access is critical for patients who are on haemodialysis (HD) and suffering from end-stage renal disease (ESRD). Arteriovenous fistula (AVF) is the ideal way of gaining HD vascular access because of its lower infection rate and associated morbidity and mortality as compared to either an arteriovenous graft (AVG) or a central venous catheter (CVC) [1, 2]. However, long-term AVF patency is a significant problem; recently, studies have revealed a one-year AVF survival rate of 40–90% [3–6]. AVF stenosis from neointimal hyperplasia leading to thrombosis in any fistula segment is the most common cause of loss of patency [5, 7, 8]. Early manifestations from physical examination (PE) include a weak fistula,
decreased arterial or increased venous pressure, limb oedema, loss of AVF collapse after arm elevation, and a decreased thrill in AVF [5, 9, 10].

Therefore, the European Society of Vascular Surgery (ESVS) Guidelines 2018 recommend surveillance of vascular access using non-invasive methods to identify stenotic lesions early so that interventions can be organized and the risk of later thrombosis mitigated [10, 11]. Furthermore, the Kidney Disease Outcomes Quality Initiative (KDOQI) 2019 guidelines recommend doing routine AVF surveillance by measuring access blood flow, monitoring pressure, or imaging for stenosis in addition to routine clinical monitoring [12].

Fistulography is the gold standard for diagnosing AVF stenosis, but it is an invasive method that has high costs, involves contrast exposure, and is not available in some HD centres. Currently, non-invasive access flow measurements are proposed, including ultrasound dilution, urea dilution, and colour Doppler ultrasonography [10, 13, 14].

There is no substantial evidence to guide the choice of a non-invasive surveillance technique. The screening algorithm of AV access flow by ultrasound dilution results in high sensitivity in the detection of hemodynamically significant stenosis [15].

Urea recirculation, which involves the calculation of access flow by inducing urea recirculation by reversing blood flow, has high sensitivity and specificity in detecting a needed intervention. It works well for low blood flow but is insensitive at high flow [13, 16]. Additionally, ultrasound dilution and urea circulation methods are strongly related to blood pressure, and it might be beneficial to calculate a ratio between measured access flow and blood pressure.

Colour Doppler ultrasonography can be used to evaluate access flow and identify stenosis sites in AVF, which is not possible with the urea and dilation technique [17]. However, colour Doppler ultrasonography is-operator dependent and time-consuming. Several studies have shown the benefit of non-invasive monitoring tools for detecting vascular access stenosis [13, 18–21]. However, no study has compared three non-invasive tools: urea dilution, ultrasound dilution, and Doppler ultrasound for use in cases of clinical suspicion for AVF stenosis. This study aimed to evaluate the utility of the different non-invasive access flow measurement methods (urea dilution, ultrasound dilution, and Doppler ultrasonography) for detecting AVF stenosis in patients on HD who have a mature AVF and are under clinical suspicion for AVF stenosis.

Methods

Study design and patients

This cross-sectional study was conducted on patients with native mature AVFs and who were receiving HD at the Siriraj Hospital Medical School, Bangkok, Thailand on January–December 2018. The definition for mature AVF was a diameter of at least 6 mm and a blood flow rate that reached 600 ml/min. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethics committees and institutional review boards approved the research protocol. All patients gave written informed consent before participating.

Physical examination (PE) was performed in our dialysis centre on 115 patients receiving HD between January and December 2018 by a HD staff nurse and 2 nephrologists. Inter-observer variability of PE was defined as 5% among staff nurses and nephrologists. We recruited patients who had features of AVF stenosis, including limb oedema, loss of AVF collapse after arm elevation, high arterial negative pressure, prolonged bleeding from a puncture site after needle withdrawal, and high venous pressures of over 200 mmHg on 3 consecutive HD runs. Other dialysis parameters were also reviewed for additional evidence (i.e., unexplained HD inadequacy and difficulty when needling). Patients suspected of having AVF stenosis underwent three non-invasive tests looking for objective evidence of stenosis and fistulography. An antegrade puncture using an 18G needle at dialysis fistula was performed, and venography was done to evaluate the patency of dialysis fistula and venous outflow and central veins. Retrograde access using a 5Fr vascular sheath at the dialysis fistula and a 5Fr catheter was used to retrogradely select pass through anastomosis to an artery. Then angiography was performed to evaluate artery, arteriovenous anastomosis, and juxta-anastomosis. Inflow stenosis was defined as any stenosis within the arterial system, artery–vein anastomosis, and juxta-anastomosis region up to the arterial site or 2 cm downstream from the arterial anastomosis. Outflow stenosis was defined as any stenosis located beyond the cannulation area downstream from the venous needle and at locations up to the atrium [22]. Significant (severe) stenosis was defined by a 50% reduction in vessel diameter compared with an adjacent segment.

AVF assessment

The protocol for investigation was as follows: each patient under clinical suspicion for AVF stenosis underwent
ultrasound dilution, urea dilution studies, and Doppler ultrasound scans in the first, second, and third week, respectively. Each test was repeated twice in consecutive HD sessions. During transonic ultrasound and urea dilution, studies were performed in the first hour of dialysis with the same blood flow rate in all patients. All patients underwent fistulography within four weeks of completion of the non-invasive tests.

A Transonic® HD monitor (Transonic, New York, USA) was used to perform ultrasound dilution. A measurement was taken twice within 30–60 min after HD initiation. Ultrafiltration was turned off during measurement in all patients. The same HD nurse who had done HD performed a urea dilution test within 30–60 min of starting HD. After line reversal, arterial (a) and venous (v) samples were drawn at a blood flow rate (Qb) of 350–400 mL/min; and a systemic (s) sample was drawn from the arterial tubing after the blood pump had been stopped. Blood urea nitrogen (BUN) concentrations were measured in all samples. Recirculation (R) and access flow (Qa) were calculated as follows:

\[
R = 100 \times \frac{(\text{BUN}_s - \text{BUN}_a)}{(\text{BUN}_s - \text{BUN}_v)} \quad (1)
\]

\[
Q_a = Q_b \times \frac{(1 - R)}{R} \quad (2)
\]

A nephrologist and a radiologist independently performed colour Doppler ultrasonography on the same day for each patient (Fig. 1). The results of access flow from all techniques were calculated and presented as a mean value and a median for symmetrical and asymmetrical data distribution, respectively. A 7–15 MHz linear transducer was used. Peak systolic velocity and AVF diameter were measured at the anastomosis, juxta-anastomosis, body, and outflow site of the AVF. Access flow (Qa) was calculated as follows:

Access flow (mL/min)

\[
= \text{Time} - \text{averaged mean velocity (cm/sec)} \times \pi \times \text{radius}^2 \times 60\,(s)
\]

Access flow measurement was performed based on a standardized protocol using a Toshiba Xario 100 (Toshiba, Tokyo, Japan) and a Toshiba PLU-704BT linear transducer with patients lying in a supine position. Waveforms of the arterial inflow and the arterial anastomosis were obtained at over 10 cm of brachial artery, which was demonstrated using transverse and longitudinal B-mode and colour flow images. Access flow measurements were done twice for each patient and average access flow was calculated from these measurements [23].

An interventional radiologist performed fistulography to evaluate vascular access from a feeding artery to a vein. AV fistula with more than 50% stenosis was defined as significant stenosis which may require angioplasty.

**Statistical analysis**

Data are presented as percentages, mean ± standard deviations (SD), or medians with a 95% confidence interval [CI]. Receiver operating characteristic (ROC) curves were analysed to determine the accuracy of the three non-invasive tests as measured using area under the curve (AUC) to
identify optimal cutoffs for continuous variables. \( p \) values less than 0.05 were considered statistically significant. SPSS version 20 software (IBM, New York, USA) was used for analysis.

**Results**

One hundred and fifteen HD patients provided written informed consent. Eighty-seven patients were excluded because they (i) failed to meet the criteria for AVF stenosis \((n = 39)\) or (ii) used AVG or CVC \((n = 48)\). The remaining 28 patients completed all baseline assessments and were enrolled in the study. Five patients were excluded due to their failure to complete all vascular access measurements. Therefore, 23 patients were enrolled in the final analysis (Fig. 2).

The 23 recruited patients were clinically suspected of AVF stenosis. The characteristics of the patients and their AVFs are summarized in Table 1. The median duration of dialysis was 5.5 years. Fourteen (60\%) of the fistulas were located in the forearm (radio cephalic) and nine (40\%) were located in the upper arm (brachiocephalic). Fifteen fistulas (65\%) revealed physically suspicious signs of AVF stenosis. Thirty-five percent of the patients showed significantly increased venous pressure during dialysis without any anomaly at PE.

The median access flows obtained through ultrasound dilution, urea dilution, and Doppler ultrasonography methods were 805, 828, and 604 mL/min, respectively. Fistulography revealed AVF stenosis in 18 patients, 12 of whom had significant stenosis (greater than 50\%). The locations of the stenosis lesions were at the juxta-anastomosis (eight patients) and the body of the venous segment (six patients); furthermore, four patients had stenosis at both juxta-anastomosis and any part of the venous segment. Median access flows in the non-significant stenosis group and in the significant stenosis group are shown in Table 2. In the significant stenosis group, ROC showed an AUC of access flow that was 0.53 (95\% CI 0.26–0.85) for ultrasound dilution, 0.63 (95\% CI; 0.32 to 0.93) for urea dilution, and 0.93 (95\% CI 0.81–1.00) for Doppler ultrasound (Fig. 3). Doppler ultrasound is a far more accurate method for detecting non-significant AVF stenosis (less than 50\%) compared to the other non-invasive methods (statistical significance \( p < 0.01\) for both ultrasound dilution and urea dilution techniques). Sensitivity and specificity in the detection of non-significant AVF stenosis by Doppler ultrasound were 80\% and 100\%, respectively (Table 3).

Using ROC curve analysis, the method with the best discriminatory capacity for diagnosis of significant AVF stenosis (more than 50\%) was found to be Doppler ultrasound which had an AUC of 0.93 (95\% CI 0.82–1.00). The other methods demonstrated an AUC of 0.74 (95\% CI 0.52–0.97) for ultrasound dilution and 0.82 (95\% CI 0.63–1.00) for urea dilution in detecting significant stenosis. Sensitivity and specificity for the diagnosis of significant stenosis of AVF by Doppler ultrasound were 100\% and 82\%, respectively. The

![Flow chart of patient recruitment](image)

**Table 1** Baseline demographic data

| Parameter                      | Value       |
|--------------------------------|-------------|
| Number of patients, \( n \)     | 23          |
| Sex male/female, \( n \)       | 16/7        |
| Age (years), mean (range)       | 63.45 (46–80) |
| Duration of HD (median years, range) | 5.5 (2–21) |
| Underlying disease              |             |
| Hypertension, \( n \) (%)       | 22 (95\%)   |
| Coronary artery disease, \( n \) (%) | 13 (56.5\%) |
| Diabetes, \( n \) (%)           | 8 (34\%)    |
| Caused of ESRD                  |             |
| Diabetes, \( n \) (%)           | 8 (34\%)    |
| Hypertension, \( n \) (%)       | 7 (30.4\%)  |
| Glomerular diseases, \( n \) (%)| 7 (30.4\%)  |
| Other, \( n \) (%)              | 1 (4.3\%)   |
| Single pool Kt/V mean ± SD      | 2.17±0.50   |
| Venous pressure (mmHg, mean ± SD)| 218±20.49  |

**Table 2** Access flow measurement by non-invasive methods

| Methods                        | Access flow (mL/min) (median with range) |
|--------------------------------|----------------------------------------|
| Ultrasound dilution            | 805 (748–1295)                         |
| Urea dilution                  | 828 (575–1,267)                        |
| Doppler ultrasound             | 604 (519–799)                          |
| Non-significant Stenosis (≤50\%) | 625 (360–850)                        |
| Significant stenosis (>50\%)   | 615 (385.32–966)                       |
|                                | 590 (399–604)                          |
sensitivity and specificity of the other methods are shown in Table 4.

In this study, PE had 80% sensitivity and 80% specificity in the diagnosis of AVF stenosis. Combining PE with non-invasive methods improved the accuracy of these methods in the diagnosis of AVF stenosis. The combinations of a positive PE with ultrasound dilution and urea dilution improved their sensitivity to 80% and 93%, respectively.

There were no differences between the two raters (nephrologist and radiologist) in terms of access flow measurement by Doppler ultrasound—their corresponding coefficients of variation (CV %) were 4.73 and 4.53, respectively. However, for the dilution method which was operated by HD staff nurses, we found a CV of 8%.

### Discussion

This cross-sectional study evaluated the characteristics of three non-invasive methods for the detection of AVF stenosis. We found that among the non-invasive tests, Doppler ultrasound had the best accuracy in detecting and locating AVF stenosis. ESVS guidelines recommend a flow measurement of arteriovenous fistulas every 3 months for hemodynamically significant stenosis that can be treated so as to prevent thrombosis and prolong the longevity of the AVF [11]. This approach has been questioned and several issues have been raised concerning the predictive accuracy of screening methods [20, 24–26]. The data from a systematic review found that a prospective surveillance of AVFs for significant stenosis when combined with a correction of anatomic stenosis could decrease the incidence of thrombosis but was not significant in preventing access loss [27, 28]. However, to evaluate the AV fistula function, several studies propose non-invasive methods for early detection and correction. Multiple papers have evaluated bedside procedures for the measurement of access flow. A previous study demonstrated that there was no significant difference in access flow measurement between the ultrasound dilution method and duplex ultrasonography [29]. Furthermore, there was no difference in access flow measurement accuracy of AV fistula and AV graft in ultrasound dilution when compared with the colour Doppler ultrasound technique [30]. Determining which tool is superior for evaluating and monitoring vascular access remains controversial [21, 31–34]. In this study, we aimed to demonstrate the accuracy of various tools for detecting AVF stenosis in a patient who had been clinically suspected of stenosis. Doppler ultrasound showed a high discriminatory capacity in the diagnosis of AVF stenosis. That said, there was variability and operator dependence. We also assessed the inter-rater agreement for Doppler ultrasound and found no significant difference between raters.

### Table 3 Diagnostic performance of non-invasive methods for non-significant stenosis of AVF (less than 50% stenosis)

| Methods               | AUC          | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-----------------------|--------------|-----------------|-----------------|---------|---------|
| Ultrasound dilution   | 0.55 (95% CI, 0.26–0.85) | 73              | 40              | 78      | 33      |
| Urea dilution         | 0.63 (95% CI, 0.32–0.93)  | 73              | 80              | 92      | 57      |
| Doppler ultrasound    | 0.93 (95% CI, 0.81–1.00)  | 80              | 100             | 100     | 80      |

### Table 4 Diagnostic performance of non-invasive methods for significant stenosis of AVF (more than 50% stenosis)

| Methods               | AUC          | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-----------------------|--------------|-----------------|-----------------|---------|---------|
| Ultrasound dilution   | 0.74 (95% CI, 0.52–0.97) | 89              | 46              | 57      | 83      |
| Urea dilution         | 0.82 (95% CI, 0.63–1.00)  | 89              | 64              | 80      | 67      |
| Doppler ultrasound    | 0.93 (95% CI, 0.82–1.00)  | 100             | 82              | 69      | 100     |
Regarding accuracy in diagnosing stenosis in AVF, the available studies have reported on both AV grafts and AVFs; in an uncontrolled, nonrandomized approach, our results suggest Doppler ultrasound is a highly accurate method for the detection of AVF stenosis [20, 22, 26, 31]. The sensitivity and specificity in this study were different from those in previous studies because our eligible patients had clinical suspicion for AVF stenosis from PE and/or had venous pressure of more than 200 mmHg. In this study, we showed that PE is highly sensitive and specific in detecting AVF stenosis in particular when combined with Doppler ultrasound.

From our study, Doppler ultrasound is useful for detecting AV fistula stenosis. PE combined with urea dilution may be an alternative method for detecting AVF stenosis when Doppler ultrasound is not available. Several studies have demonstrated the role of both urea and ultrasound dilution in the detection of recirculation and abnormal access flow [14, 15, 21, 28, 33, 35].

Our study had some limitations. Firstly, it was of a single-centred nature and had few patient numbers. Therefore, a modest number of negative results from fistulography may have affected the specificity accuracy. Moreover, we included only symptomatic patients because the investigation—especially fistulography—was quite invasive. However, the inclusion criteria for AV fistula stenosis in our study included high venous pressure, which was an early sign for detecting access malfunction. Secondly, information regarding long-term AV fistula patency was not available. Lastly, we did not demonstrate secondary patency after AVF stenosis correction. A future study that includes a large patient number may be needed to demonstrate the accuracy of the non-invasive method in detecting AVF stenosis.

Conclusion

In conclusion, access flow measurement using Doppler ultrasound is highly accurate in detecting AVF stenosis in patients under clinical suspicion for AV fistula stenosis. Doppler ultrasound combined with PE remains an essential tool for detecting AVF stenosis in patients on HD.

Author contributions SK and TS were involved in the study design. SK, WN, SR and TS contributed to data collection. SK and TS completed analysis and writing of the manuscript. SK and TS contributed to data analysis and editing of the manuscript. All the authors participated in critical reading, commenting, and final acceptance of the article. The authors read and approved the final manuscript.

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Availability of data and materials The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interest None of the authors had any conflict of interest in relation to this study.

Ethics approval Ethical approval was obtained from Siriraj Institutional Review Board, Faculty of Medicine, Siriraj hospital, Mahidol University (EC number 665/2560).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Trial registration

The study had been approved for at Thai Clinical Trial Registry (TCTR). The registry number is TCR20190325002 http://www.clinicaltrials.in.th/index.php?tp=registrals&menu=trialsearch&m=fulltext&task=search&task2=view1&id=4587

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