World Journal of Nephrology

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DOI: 10.5527/wjn.v4.i1.6

World J Nephrol 2015 February 6; 4(1): 6-18
ISSN 2220-6124 (online)

REVIEW

Combined functional and anatomical diagnostic endpoints for assessing arteriovenous fistula dysfunction

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Received: July 19, 2014
Peer-review started: July 19, 2014
First decision: August 14, 2014
Revised: November 7, 2014
Accepted: November 17, 2014
Article in press: November 19, 2014
Published online: February 6, 2015

Abstract

Failure of arteriovenous fistulas (AVF) to mature and thrombosis in matured fistulas have been the major causes of morbidity and mortality in hemodialysis patients. Stenosis, which occurs due to adverse remodeling in AVFs, is one of the major underlying factors under both scenarios. Early diagnosis of a stenosis in an AVF can provide an opportunity to intervene in a timely manner for either assisting the maturation process or avoiding the thrombosis. The goal of surveillance strategies was to supplement the clinical evaluation (*i.e.*, physical examination) of the AVF for better and earlier diagnosis of a developing stenosis. Surveillance strategies were mainly based on measurement of functional hemodynamic endpoints, including blood flow (Q_a) to the vascular access and venous access pressure (VAP). As the changes in arterial pressure (MAP) affects the level of VAP, the ratio of VAP to MAP (VAPR = VAP/MAP) was used for diagnosis. A Q_a < 400-500 mL/min or a VAPR > 0.55 is considered sign of significant stenosis, which requires immediate intervention. However, due to the complex nature of AVFs, the surveillance strategies have failed to consistently detect stenosis under different scenarios. VAPR has been primarily developed to detect outflow stenosis in arteriovenous grafts, and it hasn't been successful in accurate diagnosis of outflow lesions in AVFs. Similarly, AVFs can maintain relatively high blood flow despite the presence of a significant outflow stenosis and thus, Q_a has been found to be a better predictor of only inflow lesions. Similar shortcomings have been reported in the detection of functional severity of coronary stenosis using diagnostic endpoints that were based on either flow or pressure. This limitation has been associated with the fact that both pressure and flow change in the presence of a stenosis and thus, hemodynamic diagnostic endpoints that employ only one of these parameters are inherently prone to inaccuracies. Recent attempts have resulted in development of new diagnostic endpoints that can combine the effects of pressure and flow. These new hemodynamic diagnostic endpoints have shown to be better predictors of functional severity of lesions as compared to either flow or pressure based counterparts. In this review article, we discussed the advantages and limitations of current functional and anatomical diagnostic endpoints in AVFs.

Key words: Arteriovenous fistula; Dysfunctional arteriovenous fistulas; Stenosis; Surveillance; Flow rate;

Pressure

Core tip: Current surveillance strategies are based on either flow (Q_a) or pressure (VAPR) measurements. The Q_a has only shown to be a good predictor of inflow stenosis in arteriovenous fistulas (AVFs). The VAPR was primarily developed to detect outflow stenosis in arteriovenous grafts and has shown to be a poor predictor of stenosis in AVFs. These limitations have been associated with the fact that both pressure and flow change in the presence of a stenosis and thus, hemodynamic diagnostic endpoints that employ only one of these parameters are inherently prone to inaccuracies. Thus, diagnostic endpoints that can combine both effects of pressure and flow can provide better assessment of stenosis severity in AVFs.

Rajabi-Jaghargh E, Banerjee RK. Combined functional and anatomical diagnostic endpoints for assessing arteriovenous fistula dysfunction. *World J Nephrol* 2015; 4(1): 6-18 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i1/6.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i1.6

INTRODUCTION

Around 600000 Americans have end-stage renal disease, among whom approximately 415000 patients are being treated by hemodialysis through surgically created vascular access (VA)[1]. Failure in maintaining a functional VA has been the leading cause of hospitalization in the hemodialysis population and has resulted in more than $1 billion annual cost to the health care system in the United States[1]. The most preferred form of the VA is the arteriovenous fistula (AVF); however, this type of access has still a significantly high failure rate (20% to 50% in the United States). AVF failure requires placement of central venous catheter which is the least desirable form of VA due to its significant morbidity and mortality[2,3].

Thrombosis is the major cause of failure in AVFs, which requires endovascular or surgical intervention of the access[4-7]. The majority of AVFs with thrombosis had an underlying stenosis[8-10]. A developing stenosis gradually reduces the blood flow to the access and alters the pressure in the AVF. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)[11,12] has recommended routine surveillance to detect the stenosis early enough to allow preemptive interventions. Current surveillance strategies[13] include device-based measurements, such as blood flow to AVF or venous access pressure. Under the current KDOQI guidelines[12], an AVF with blood flow rate < 400-500 mL/min or a ratio of venous access pressure to main arterial pressure > 0.55 has to be referred to fistulography for assessing the grade and location of the stenosis.

The accuracy of the current surveillance strategies for detecting a stenosis is debatable, especially in AVFs[14-17]. These limitations can be associated with specific pathophysiology of AVFs[8,10]. AVFs can have a significant stenosis and still maintain a relatively high blood flow[18]. In such scenarios, blood flow to AVF gradually reduces over time. Thus, sequential (longitudinal) measurements of Q_a over time were expected to provide better clinical decision making than a single Q_a measurement. Also in case of a significant outflow stenosis, the venous access pressure may retain its normal levels at the cannulation site due to development of downstream collateral pathways[8,10,15,19]. It is noteworthy that similar shortcomings have also been reported in functional (hemodynamic) diagnosis of coronary stenosis. Such diagnostic endpoints for coronary artery disease were either based on pressure or flow; however this neglects the fact that both flow and pressure change in the presence of a stenosis. Recent studies have attempted to shift the current paradigm into introducing new diagnostic endpoints that can account for both pressure and flow variation for assessing the functional severity of a stenosis[20-24]. This review article describes the advantages and limitations of current surveillance strategies including functional and anatomical diagnostic endpoints in AVFs.

This review has covered the most important and pioneering studies that have reported the use of hemodynamic and anatomical endpoints for assessing the AVF functionality. We performed a literature search using PubMed, Medline, and Google Scholar for studies written in English from 1995 to 2014. We used the following search terms: arteriovenous fistula; surveillance strategies; stenosis; flow rate; pressure; coronary flow reserve; fractional flow reserve; pressure drop coefficient; resistance index, in combination with the exploded term "diagnosis". The references were included based on their relevance and contribution to address the challenges and future directions in the diagnostic field of stenosis linked to AVF.

AVF MATURATION, FUNCTIONALITY, AND DYSFUNCTION

According to the guidelines of NKF-KDOQI[11,12], the venous segment of a matured AVF should follow the rules of sixes: a blood flow > 600 mL/min, a diameter > 6 mm, a depth of around 6 mm, and at least 6 cm of a straight segment for cannulation. Normally, a minimum of 28 d (d: days) should be allowed for AVF maturation before performing the first needling; however, this time could be extended if the AVF fails to mature. Once an AVF is used for cannulation, it should be able to provide a minimum flow rate of 350-450 mL/min during 3-5 h of dialysis without recirculation, a characteristic that defines a functional AVF. A dysfunctional AVF is, however, defined as an access that is not able to provide the minimum flow during dialysis and is clinically identified by variations in thrill/bruit, difficult cannulation, recirculation, excessive bleeding from the venopuncture sites and

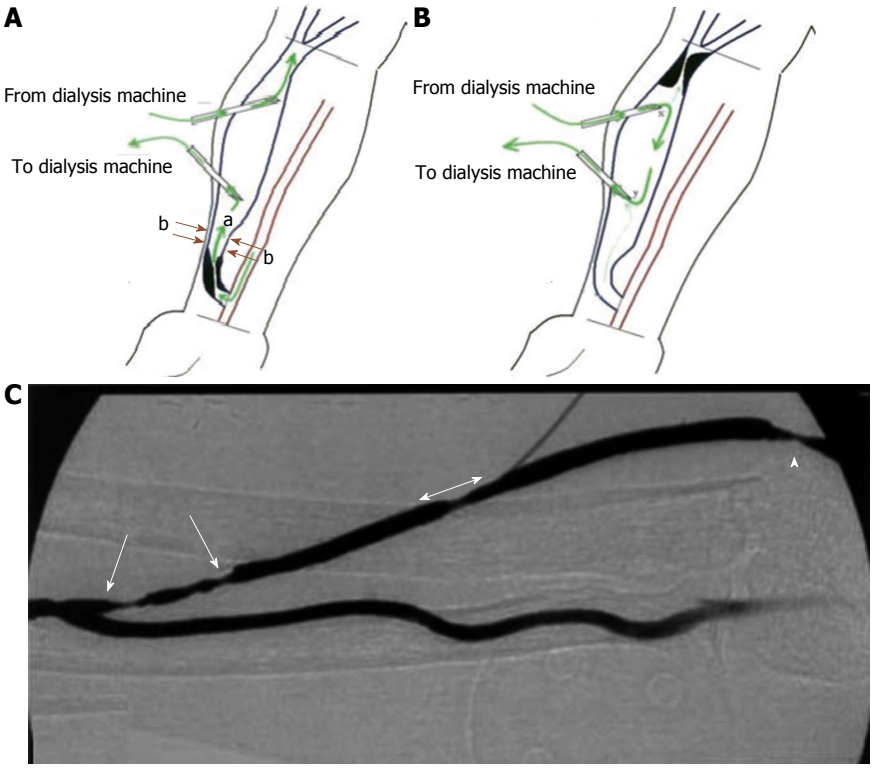

Figure 1 Schematic of the locations of (A) inflow stenosis, and (B) outflow lesion with respect to the anastomosis and cannulation sites[27]. The (green) arrows in A and B represent the direction of blood flow within the arteriovenous fistulas (AVF) and the dialysis needles; B: Depicts a recirculation condition under which due to significant outflow stenosis the blood flow from dialysis machine returns back to dialyzer; C: An angiographic picture of an AVF with multiple inflow stenoses (single head arrows) and outflow stenosis (double head arrow and the arrow head). Reprinted from Asif *et al*[25] and Fahrtash *et al*[27], with permission.

ultimately thrombosis. Thrombosis, the main cause of access failure, is usually preceded by the development of an underlying stenosis. Consequently, the detection of stenosis in AVFs before thrombosis could offer a strategy to improve AVF survival by early intervention.

Stenosis in vascular access

Stenosis in vascular access can be categorized into two main groups of inflow and outflow stenoses[9,25]. An inflow stenosis is a lesion that occurs around the anastomosis and proximal to the venous needle, while an outflow stenosis is located further from anastomosis and distal to the venous needle. The stenosis location has been shown to be dependent on the type of access. Radio-cephalic AVFs are more prone to inflow stenosis, whereas outflow stenosis is more likely to occur in the brachio-cephalic AVFs. In contrast to AVFs, the arteriovenous grafts (AVGs) mostly develop outflow stenosis[26]. Figure 1A[27] and 1B[27] show the schematics of an inflow and outflow stenosis with respect to the anastomosis and cannulation sites, respectively, while Figure 1C[25] shows an angiographic picture of an AVF with multiple inflow and outflow lesions. All the clinical monitoring and surveillance programs have been designed to predict the development of a significant stenosis early enough to allow preemptive corrections of AVFs. Despite the importance of stenosis severity, its definition is still controversial[27,28]. A significant stenosis has been defined as a local reduction of > 50% in luminal diameter as compared to the adjacent normal vessel. This definition is inherently biased and is dependent on the location of the reference cross-section in the adjacent normal vessel (Figure 2[27]). Also, imaging techniques such as Doppler ultrasound only provides a 2D illustration of a 3D lesion, while other imaging modalities such as computed tomography (CT)-scan or magnetic resonance imaging (MRI) are expensive and not readily accessible. Despite these drawbacks, the stenosis severity still serves as the most important endpoint to direct the clinical decision making for the timing of further interventions.

MONITORING AND SURVEILLANCE PROGRAMS

Monitoring strategies mainly include physical examination (PE) and other clinical evidences of access dysfunction for stenosis detection, while surveillance programs were intended to supplement clinical monitoring by measuring variations in blood flow rate and venous access pressure. The PE, backbone of all screening programs, is a readily available and cost-effective tool to detect inflow and outflow stenosis in AVFs. PE has proved to be an accurate predictor of venous stenosis, and several studies have concluded that PE should be the part of all screening programs[29]. The only drawback of PE is the need for

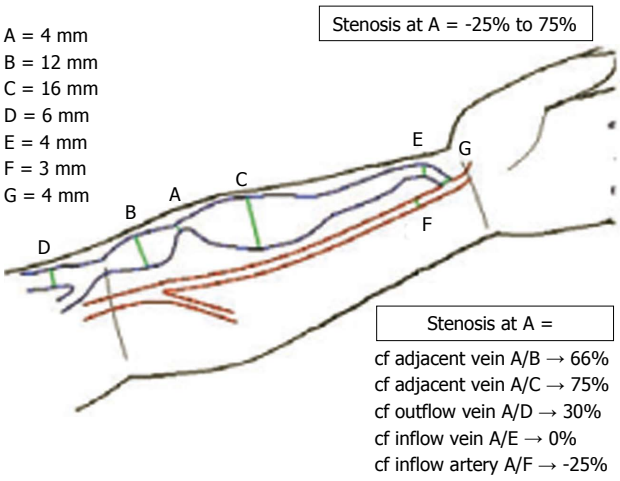

Figure 2 Dependency of stenosis severity to the location of reference cross sec-tion[27]. In this figure stenosis is located at A. Depending on the location of the reference cross-section, one can calculate a stenosis severity ranging from -25% to 75%. The -25% diameter changes represents a case in which the minimum diameter in the arteriovenous fistulas circuit has happened elsewhere than cross-section A. Reprinted from Fahrtash *et al*[27], with permission.

trained and experienced dialysis personals, leading to variability in decision making.

FUNCTIONAL (HEMODYNAMIC) ENDPOINTS

A developing stenosis eventually reduces blood flow and alters pressure profiles in the vascular access. Effects of stenosis on hemodynamic (blood flow and pressure) profiles are dependent on the type of vascular access (AVF or AVG) and the location of stenosis (inflow, outflow, or both). Therefore, monitoring the changes in flow and pressure can provide useful functional information on the severity of the underlying stenosis. NKF-KDOQI guidelines have recommended that both AVGs and AVFs undergo routine surveillance for blood flow and venous access pressure measurements.

Flow surveillance

The blood flow (Q_a) measurement is currently the gold standard of all surveillance programs. The Q_a measurement has been shown to be fairly reproducible both within and between the dialysis sessions. Blood flow rate can be measured by either indirect techniques such as ultrasound dilution or direct methods such as Doppler ultrasound, or MRI. The latter can provide valuable information about the location and severity of stenosis; however, it has the disadvantage of being more expensive and time consuming. Figure 3[8,9] shows a sample velocity pulse obtained from Doppler ultrasound as well as an example of detected stenosis using such technique. Although Q_a has been widely used as the most reliable surveillance strategy, there are numerous different Q_a thresholds for clinical decision makings in AVFs[30]. A wide range of Q_a from 300 mL/min to 900 mL/min[31-35] has been reported in different studies as the threshold for intervention. Under current KDOQI guidelines, an AVF should be referred for fistulogram when Q_a < 400-500 mL/min.

Polkinghorne *et al*[15] looked at the effectiveness of the KDOQI guideline for Q_a (< 500 mL/min) to detect a significant stenosis in 137 patients with AVF. These patients were randomly assigned to a control group receiving standard-of-care clinical treatment and Q_a surveillance group that received the same treatment as the control group plus monthly Q_a measurement. Under the normal treatment, an AVF was referred to fistulography if any of the following occurred: (1) raised venous dynamic pressure; (2) reduced blood pump flow; or (3) excessive bleeding from venopuncture site. They showed that the likelihood of stenosis detection in the Q_a surveillance group was two times but insignificant in relation to the control group, with a trend for a significant stenosis to be detected earlier. However, they also showed that over reliance on only blood flow threshold < 500 mL/min could misdiagnose some cases with positive sign of stenosis under standard-of-care treatment and angiography. They concluded that this misdiagnosis could be due to lack of understanding of the relationship between the blood flow in the vascular access and a developing stenosis.

Tessitore *et al*[33] tested different surveillance techniques such as PE, venous access pressure ratio, recirculation, and Q_a on a random population of 119 matured AVFs to find the ability and accuracy of these methods in detecting a significant stenosis. In addition to the surveillance methods, all patients underwent angiography to identify the grade of stenosis in the AVFs. Almost 50% of the AVFs had a significant stenosis either upstream of venous needle (inflow stenosis) or downstream of venous needle (outflow stenosis) or at both sites. A combination of PE and Q_a < 650 mL/min was able to provide a moderate-to-excellent tool to detect inflow stenosis with sensitivity of 85% and specificity of 89%. However, Q_a was not determined to be an adequate predictor of outflow stenosis. Therefore, they concluded that accuracy of Q_a to detect a significant stenosis is strongly dependent on the location of lesion.

Moreover, a randomized study[36] on 58 patients showed that preemptive intervention for AVFs with a Q_a > 500 mL/min results in 3-fold reduction in thrombosis and loss of vascular access as compared to the KDOQI guideline (Q_a < 400-500 mL/min) that is more suitable to detect a hemodynamically significant stenosis. Therefore, the current Q_a surveillance for AVF needs modification for improved detection of a significant stenosis well before it adversely affects the functional or hemodynamic condition.

Pressure surveillance

Besarab *et al*[37,38] proposed the use of venous access pressure to predict the stenosis severity in AVGs. Figure 4[38] shows the schematic for the measurement of venous access pressure using pressure transducers at the

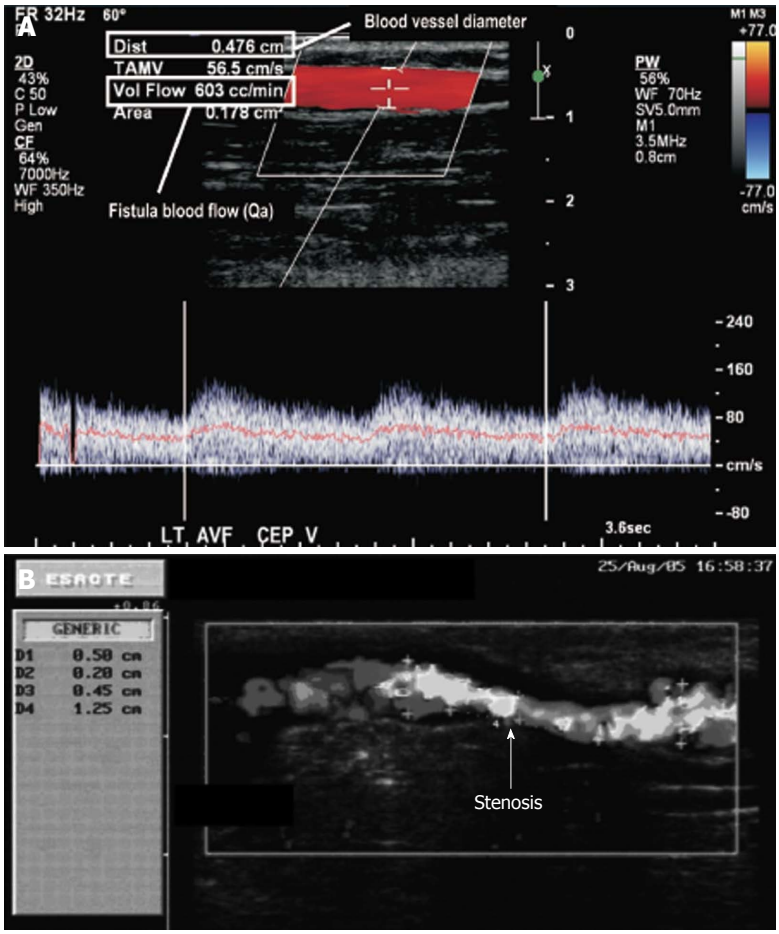

Figure 3 (A) Velocity pulse from Doppler ultrasound, and (B) detection of stenosis and estimating its grade using Doppler ultrasound[8,9]. AVF: Arteriovenous fistula. Reprinted from Campos *et al*[8] and Feddersen *et al*[9], with permission.

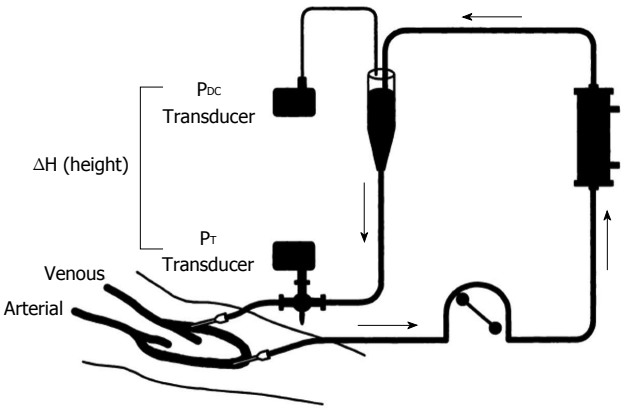

Figure 4 Schematic for measurement of venous access pressure in an arteriovenous graft using pressure transducers located at the venous needle and drip chamber[38]. Reprinted from Besarab *et al*[38], with permission.

venous needle and also at the drip chamber of dialysis circuit. Further with the development of this technique, the ratio of venous access pressure (VAP) to the mean arterial pressure (MAP) was used for detecting the stenosis severity (VAPR = VAP/MAP). A VAPR > 0.55 was associated with a clinically significant stenosis. In a prospective study, Besarab *et al*[39] monitored the variation of VAPR on 832 patients among whom 80% of accesses were AVG. The VAPR > 0.55 was found to be an excellent criterion for angiographic referral and intervention of a clinical stenosis in AVGs. It should be noted that VAPR was primarily developed to detect outflow stenosis in AVGs and by design was unable to detect an inflow stenosis[10]. It should be noted that AVGs are more prone to develop an outflow stenosis than an inflow lesion. In case of an inflow stenosis pressure drops in the access and consequently, VAPR remains below the cut-off level. Thus VAPR has been unsuccessful to detect the inflow lesions in AVGs.

Although, the VAPR is a promising parameter in AVGs[13,18,39,40], it has failed to show much advantage in assessing the functionality of AVFs[8,9,15]. This assertion originates from the fact that there is a fundamental difference between AVFs and AVGs. The AVG is essentially a single tube that connects the artery to vein, and thus, all the blood that enters the arterial anastomosis has to exit from the venous anastomosis. Therefore, any abnormal elevation in the pressure can be associated with the formation of stenosis mainly in the outflow segment. In contrast, the VAPR may show lesser variation while a stenosis is developing in an AVF because of the collateral pathways (accessory or collateral veins) that provide an alternative route to bypass the significant stenosis. Consequently, the flow in

the upstream venous segment of AVFs may not change even in the presence of downstream significant stenosis. In other words, the VAPR may undergo minimal changes as the flow can occur due to presence of downstream collateral channels.

The effect of stenosis on the flow and pressure fields is dependent on the location of stenosis. In general, an outflow stenosis causes an increase in the venous access pressure, while the access flow decreases over time. This is particularly more evident in an AVG than an AVF. In such scenario, an AVF can maintain a relatively high flow rate with almost unchanged pressure levels due to the development of collaterals. In the case of an inflow stenosis venous access pressure either remains stable or can decrease with the reduction in access flow under adverse remodeling. Therefore, pressure monitoring alone may not be able to detect such inflow stenosis, while it can be detected by sequential flow measurements and PE.

ANATOMICAL ENDPOINTS

Once an access is diagnosed for a significant stenosis either based on the standard-of-care clinical treatment or any of the functional surveillance strategies, a fistulogram is acquired to determine the grade and location of stenosis. However, as discussed earlier, there are a few criticisms to the current measurement protocol of the stenosis severity based on a fistulogram. These include: (1) fistulogram provides only a 2D illustration of 3D vessel; and (2) stenosis definition is biased to the location of the reference cross-section in the adjacent normal vessel for which the diameter varies a lot.

For example in a recent study, Fahrtash *et al*[27] criticized the current definition of stenosis severity and showed that, stenosis can have a wide range of severity from -25% to 75% reduction in luminal diameter based on the location of reference cross-section (Figure 2). Therefore, they hypothesized that a significant stenosis can be determined based on the absolute minimum diameter in the AVFs. They divided 170 radio-cephalic AVFs into two groups: dysfunctional (n = 93) and functional (n = 77) AVFs. The absolute minimum diameters of two groups were measured using grayscale and color ultrasound. They found that a diameter of 2.7 mm can be a good cutoff value to distinguish a functional radio-cephalic AVF from a dysfunctional one with 90% sensitivity and 80% specificity. Thus, it was concluded that a minimum diameter can be a more accurate measure to decide on the dysfunctionality of an AVF. However, this study was limited to only radio-cephalic AVFs and thus, more studies are needed to determine the critical minimum diameter for other types of AVFs.

Other studies[19,41-43] have primarily introduced the diameter as a pre-operative factor to predict if an AVF will mature. Current guidelines suggest a minimum diameter of 2 mm for successful AVF creation at wrist, but agreement on minimal diameter for other sites is lacking[19]. Lauvao *et al*[42] evaluated 158 patients undergoing initial dialysis access creation with native AVF. Three types of AVFs were created in these subjects including posterior radiocephalic AVF (n = 24), wrist radiocephalic AVF (n = 72), and brachiocephalic AVF (n = 62). Using multivariate logistic regression analysis, a vein diameter > 4 mm was found to be the only independent predictor of AVF maturation. However, a previous study by Wong *et al*[44] on 46 patients with initial radio-cephalic fistula suggested a diameter > 1.6 mm as the predictor of successful maturation of AVF. Therefore, despite its significance, there is still not a uniform agreement on the minimum diameter of AVF that can assist the clinical decision makings.

OTHER FUNCTIONAL ENDPOINTS

In addition to flow, pressure, and anatomical endpoints, wall shear stress has also been shown to have a strong correlation with functionality of AVFs. A multifold increase in blood flow rate after the AVF placement results in an extensive raise in the wall shear stress (WSS) levels acting on the luminal surface of the fistula. In order to accommodate for the marked increase in the hemodynamic stresses, the arterial and venous segments of the AVFs undergo structural changes such as vasodilation and wall hypertrophy[45-48]. These compensatory responses, also known as remodeling, attempt to regain the baseline levels of hemodynamic stresses (pre-surgery condition) in the vessels. Arterial remodeling in AVFs is mainly characterized by dilation and intima-media hypertrophy (outward hypertrophic remodeling)[49]. However, this adoptive remodeling in the venous segment can be interrupted by aggressive formation of neointimal hyperplasia, which can result in an undesired hypertrophy (thickening of the venous wall in the inward direction) and later venous stenosis, the major cause of failure in the AVFs. Therefore, monitoring the WSS levels can provide useful information on the functionality status of the AVFs.

Rajabi-Jaghargh *et al*[50] studied the linkage between the longitudinal changes in WSS and the luminal dilation for the AVFs in a pig model. Changes in the WSS levels within the AVFs were evaluated from the computational fluid dynamics models of the fistulas that were developed based on the acquired CT-scan and Doppler ultrasound data of the pigs at 2 d, 7 d, and 28 d post surgery time points. It was found that the slope of changes of WSS over time [τ' = ($WSS_{28\ d\ or\ 7\ d}$ - $WSS_{7\ d\ or\ 2\ d}$)/(time difference)] can be used to assess the functionality status in AVFs. The τ' for the AVFs with favorable remodeling (FR), as shown in Figure 5A[50], was negative between all the successive time-points representing a consistent decrease in the WSS levels over time. In contrast, for the AVFs with adverse remodeling (AR), Figure 5A, the τ' at all the successive time-points were positive showing that WSS levels were

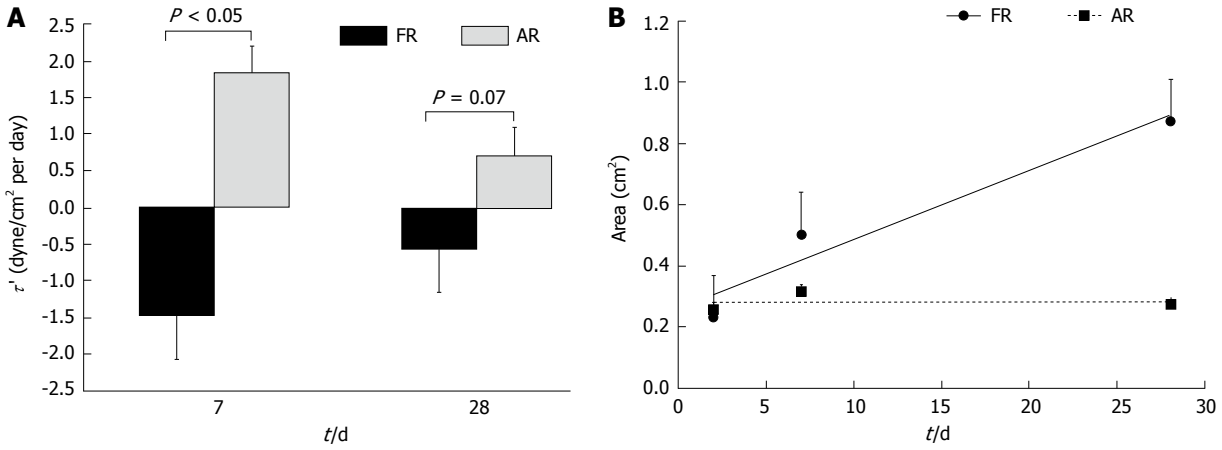

Figure 5 Variation in (A) temporal gradient of wall shear stress and (B) temporal gradient of luminal area of the venous segment for arteriovenous fistulas with favorable remodeling and adverse remodeling over time[50]. FR: Favorable remodeling; AR: Adverse remodeling. The *t*/d in the x axis stands for time (days). Reprinted from Rajabi-Jagahrgh *et al*[50], with permission.

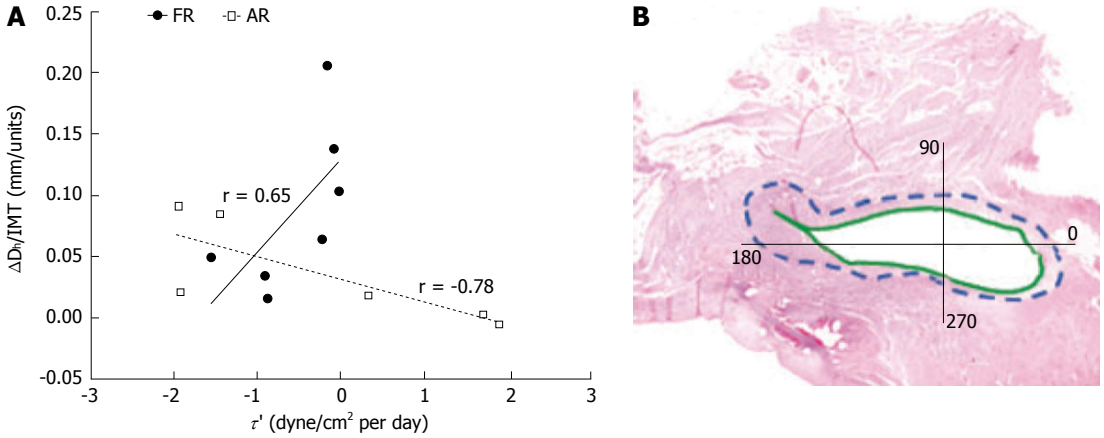

Figure 6 (A) Variation in morphological changes of the venous segment with respect to corresponding temporal gradient of wall shear stress (τ') for arteriovenous fistulas with favorable remodeling and adverse remodeling[51]. Morphological changes were quantified by calculating the ratio of differences in luminal diameter of venous segment over time (ΔD_h) to the corresponding amount of intima-media thickening (IMT). The IMT was calculated from (B) histology analysis using hematoxylin and eosin (H and E). The IMT was calculated as the average of intima-media thicknesses at four quadrants of each H and E staining slide. FR: Favorable remodeling; AR: Adverse remodeling; AVFs: Arteriovenous fistulas. Reprinted from Rajabi-Jagahrgh *et al*[51], with permission.

increasing over time for this group. These opposite patterns of WSS over time were accompanied with distinct remodeling behaviors within the two groups. The luminal area of the venous segment for the FR increased over time (Figure 5B), while for the AR the luminal area remained unchanged or reduced.

Also, in another study[51] by the same group, they showed that the temporal changes in shear stress can be correlated with morphological changes in the venous segment (Figure 6A). The morphological changes were quantified with the ratio of differences in diameter between successive time points (ΔD_h) by the amount of intima media thickness (IMT). The IMT was obtained from histology analysis (Figure 6B). The τ' showed distinct correlation between the AVFs with FR as compared to the ones with AR (Figure 6A). The positive τ' in the AR group was associated with the largest amount of IMT and lowest or negative ΔD_h, which also revealed stenosis formation in the venous segment. In contrast, the negative τ' was shown to be associated with relatively larger ΔD_h and larger IMT. This showed that the IMT in the AVFs with FR was in the outward direction as compared to the inward hypertrophy in AR group. Therefore, it was concluded that the increase in WSS of the venous segment of an AVF over time can be associated with adverse remodeling and reduced functionality, while the decrease in WSS over time can be considered a sign of favorable remodeling.

Although WSS has a key role on remodeling behavior and functionality of AVFs, the complexities and limitations associated with the accurate calculation of WSS under clinical settings have made it an undesirable clinical endpoint for surveillance strategies. Therefore, the main focus of this review is to introduce new diagnostic tools that can be readily available under current clinical settings such as flow, pressure, and anatomical endpoints. These endpoints, especially flow and pressure, have also been the main focus of surveillance strategies. However, as mentioned earlier the ability of current surveillance strategies to predict the functionality

status of AVFs has been controversial. This limitation can be associated with the fact that Q_a is based on only flow measurements, while the VAPR is a pressure based parameter. However, it may be noted that both flow and pressure change under a developing stenosis. Therefore, relying on parameters that are either based on pressure or flow can result in inaccurate and less than optimal decision making outcomes. Consequently, there is a need for new functional diagnostic endpoints that can combine both effects of pressure and flow.

FUNCTIONAL DIAGNOSTIC PARAMETERS FOR CARDIOVASCULAR AND RENAL STENOSIS

Adequacy of diagnostic tools that are based on either pressure or flow has been one of the major challenges for assessing the functional severity of stenosis in vasculatures such as coronary and renal arteries[52,53]. In this section, the limitations of current hemodynamic (pressure or flow) based endpoints for detecting the cardiovascular and renal stenoses will be discussed. Also, the combined functional (pressure and flow) endpoints for better detection of stenosis in vasculatures will be introduced.

Existing cardiovascular and renal diagnostic endpoints

Currently, fractional flow reserve (FFR; a pressure ratio) and coronary flow reserve (CFR; a flow ratio) are the two gold standards to assess the functional severity of a stenosis in coronary arteries[54]. FFR is the ratio of mean pressure distal to a stenosis to the mean proximal pressure under hyperemic condition. CFR is the ratio of blood flow rate to a diseased vessel under hyperemic condition to the corresponding basal (non-hyperemic or resting) flow. The values of FFR and CFR decrease as the stenosis severity increases. However, both FFR and CFR are affected not only by the stenosis severity but also by distal microvascular flow resistance that can increase under left ventricle hypertrophy, chronic or acute ischemia, diabetes mellitus, and other disease conditions[55-57]. If microvascular resistance is abnormal (high), then CFR decreases while FFR tends to increase. Under such scenario, FFR may be incorrectly above the cut-off (0.75-0.8) range despite the existence of a significant stenosis[58,59]. This may lead to inaccurate diagnosis which can result in either delay or missing of intervention procedure. Similar limitations exist for current KDOQI surveillance strategies to detect an outflow stenosis. Also, in the presence of collateral channels both CFR and FFR increase which result in uncertainty in diagnostics[60]. This is also similar to the scenario of an outflow stenosis with developed collateral channels in AVFs. These limitations have been associated with the inherent inaccuracies of current diagnostic parameters to detect stenosis severity that are based on either pressure or flow measurements. Such gap has resulted in recent attempts to introduce better diagnostic tools that can combine the effects of pressure and flow[61-64]. The new diagnostic endpoints rely on fluid dynamics principals that are based on non-linear relationship between pressure and flow in the presence of a developing stenosis.

Pressure-flow relationship in stenosed vessels

Based on fluid mechanics fundamentals, pressure drop for an incompressible (blood) flow inside a vessel is a function of frictional forces (viscous losses) and losses due to momentum changes. The latter can be induced by variation in luminal diameter (or area) of the vessel (*i.e.*, as a result of a stenosis), or presence of bends, bifurcations, anastomosis, and, *etc*. The viscous forces are linear function of flow, while the momentum changes have quadratic (non-linear) relationship with flow. In general, the pressure drop-flow relationship can be written as below:

$$\Delta p = Av + Bv^2 \quad (1)$$

where A and B represent the coefficients of viscous losses, and losses due to momentum changes, respectively. Equation 1 can be also written in a more general form as below:

$$\Delta p = kv^n \quad (2)$$

where n can vary between 1 and 2. The exponent in this relationship is of specific importance. For a fully developed laminar flow in a straight vessel, viscous losses are the main component of pressure drop. For such flows, n is nearly equal to 1. However, if the momentum of flow changes due to change in luminal diameter (*i.e.*, as a result of a stenosis), or due to existence of bends, bifurcations, or anastomosis, then the exponent of Δp-v relationship will become greater than 1. As the exponent becomes closer to 2, the contribution of momentum changes to pressure drop become more pronounced.

Using analytical formulations, Rajabi-Jaghargh *et al*[65] have shown that at early stages of stenosis, viscous losses are the most dominant component of pressure drop and n stays closer to 1. However, as the stenosis severity increases from 64% to 90% area stenosis the contribution of momentum changes to pressure drop becomes more pronounced and n will be > 1.5. Figure 7[65] shows the contribution of viscous losses and losses due to momentum changes to the total pressure drop in a stenosed artery with the increase in the percentage area stenosis. The n is equal to 1.5 at the point where the viscous losses and momentum changes contribute equally to the total pressure drop. For n < 1.5, the contribution of viscous losses are more, while losses due to momentum changes are more pronounced for n > 1.5. In case of an AVF, anastomosis segment imposes a local pressure loss due to momentum changes (blood flow acceleration in the bend), and thus Δp-v relationship is expected to have an exponent > 1. Although the Δp-v relationship does not directly help us to evaluate the functionality of an AVF, analyzing the exponent of Δp-v

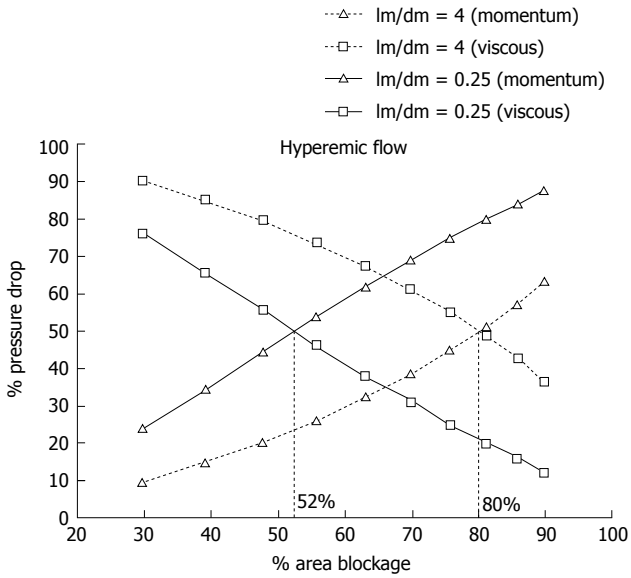

Figure 7 Contribution of viscous losses and losses due to momentum changes to the total pressure drop in a stenosed coronary artery with the increase in the percentage area stenosis[65]. Here, the pressure drop values at different stenosis severity were ob-tained under the corresponding hyperemic flow for coronary arteries. Also, lm and dm represent the length of stenosis throat and diameter of throat, respectively. Reprinted from ref. [65], with permission.

relationship can identify the contribution of viscous or momentum losses to the total pressure drop and the underlying geometrical variations (diameter or area change) in the AVF.

COMBINED FUNCTIONAL DIAGNOSTIC ENDPOINTS

Based on the pressure-flow relationship in stenosed vessels, the new functional diagnostic parameters can be defined as (1) resistance index, which represents the linear scaling of pressure drop with the velocity at the proximal artery ($R = \Delta p/v$); and (2) pressure drop coefficient, which is a pressure drop normalized by the dynamic pressure at the proximal artery ($C_p = \Delta p/(0.5\rho v^2)$, where ρ is blood density). The resistance index would be more helpful to predict a developing stenosis in early stages where *n* is closer to 1, while the pressure drop coefficient becomes more important as the stenosis becomes more severe over time in which case *n* is closer to 2. Both R and C_p have been shown to be better predictors of the functional severity of coronary stenosis under the limiting scenarios (*i.e.*, micro-vascular disease and collateral channels) as compared to FFR and CFR, the current gold standards[66-69].

Combined functional diagnostic endpoints in AVFs

The new functional diagnostic endpoints (resistance index, *R*, and pressure drop coefficient, C_p) have been recently[70] used in a pilot study on a pig model. It was shown that these parameters are capable of detecting the very early signs of a developing stenosis in AVFs. In this study, six AVFs were created between the femoral arteries and veins of 3 pigs, each pig having two AVFs on either limb. The variation in flow rates and geometries of the AVFs were studied at three post-surgery time points (2 d, 7 d, and 28 d) over about one month using Doppler ultrasound and CT-scan techniques. Also, computational fluid dynamics were used to calculate the pressure and velocity profiles for all the AVFs at every time points. Time averaged pressure difference between the proximal artery and outflow vein in conjunction with the average velocity at proximal artery were used to calculate C_p and *R* in AVFs. During the first week, all AVFs attained favorable remodeling[50,51] characterized by dilation, significant increase in flow rate, unchanged pressure drop, reduction in severity of local stenosis, and some amount of thickening due to the development of intimal hyperplasia. These changes were associated with the reduction in C_p and R levels over the first week (Figure 8).

In contrast, from 7 d to 28 d some of the AVFs showed significant dilation, while others experienced minimal changes in the mean diameter. During this period, the amount of thickening was also doubled in all the AVFs. Therefore, the minimal dilation and high amount of IMT from 7 d to 28 d for some AVFs resulted in adverse remodeling characterized by inward hypertrophy in those AVFs. On the other hand, the AVFs with significant dilation and venous wall thickening underwent positive remodeling with outward hypertrophy. Over this time period (7 d-28 d), the increase in average diameter and flow rate were minimal as compared to the first week, while the pressure drop increased for 50% of its baseline value. Also, the severity of the local stenosis, measured by area reduction, in AVFs (Figure 8A[70]) increased to 41.7% ± 8.3% which was below the clinically significant level (= 75% area stenosis). Corresponding to these changes, C_p and *R* (Figure 8B[70]) increased considerably over this time period. It was concluded that assessing the AVF functionality based on only diameter or flow rate could be misleading because they may not reveal complete information regarding the developing stenosis. However, C_p and *R* significantly increased over this time period and showed better delineation of stenosis severity. Thus, C_p and *R* could better assess the functionality of an AVF. However, this study was limited to relatively small number of data points and thus, studies with larger population and longer duration are needed to better determine advantages of the new combined pressure-flow diagnostic endpoints over the current gold standards.

Bedside measurement of new functional diagnostic endpoints

It should be noted that all the pressure-flow parameters that are needed to calculate C_p or *R* can be measured under current clinical settings. Velocity at the proximal artery can be measured through Doppler ultrasound probes and the pressure drop can be measured from the pressure readings at the cannulation sites during

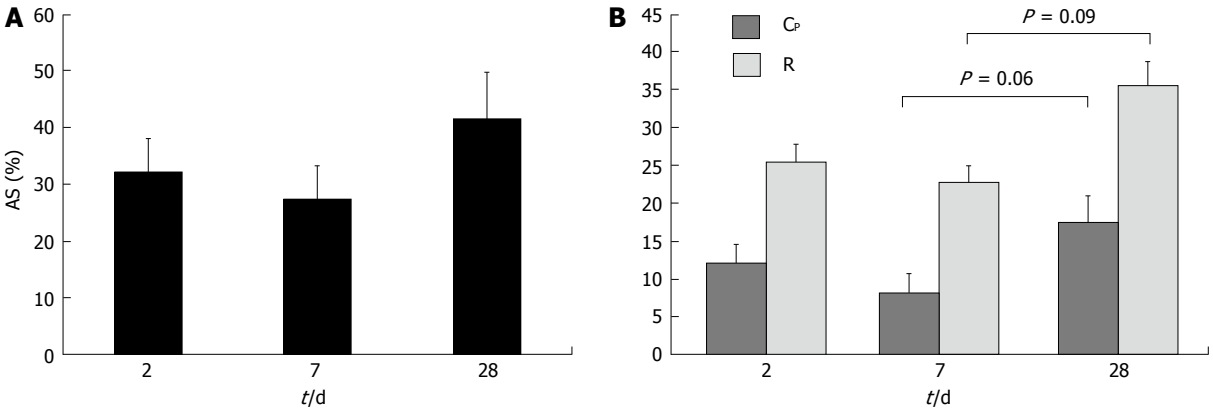

Figure 8 Variation of (A) percentage area stenosis and (B) pressure drop coef-ficient and resistance index over time for arteriovenous fistulas created in a pig model[70]. AS: Area stenosis; C_p: Pressure drop coefficient; R: Resistance index. The *t*/d in the x axis stands for time (days). © 2014, Copyright the Authors. Artificial Organs, © 2014 International Center for Artificial Organs and Transplantation and Wiley Periodicals, Inc.

the dialysis treatment. In the case of an inflow stenosis both *R* and C_p increases as pressure drop increases and flow rate decreases. Thus, both *R* and C_p are capable of detecting a developing inflow stenosis. If stenosis occurs downstream of the venous cannula (outflow stenosis) in AVFs, the pressure readings can show either lower or unchanged values of pressure drop over time, which does not reflect the presence of downstream stenosis. This is because of the development of collateral channels at the outflow stenosis area in AVFs. This shortcoming has been the major criticism to the current pressure surveillance program in which the AVF patency is assessed based on only pressure ratios at the outflow venous cannula and proximal artery. In such scenarios, if the venous flow rate decreases, both C_p and *R* begin to increase. It is noteworthy that irrespective of Δp status (numerator), as C_p has inverse quadratic relation with flow, any reduction in flow shows non-linear and pronounced increase in C_p as compared to *R*. Therefore, *R* and C_p are also capable of detecting an outflow stenosis. Thus, combining the flow and pressure data in the functional diagnostic endpoints could improve the ability of these parameters in assessing the patency of AVFs.

Limitations

The new functional diagnostic endpoints have not been tested for patient population. Thus, multi-central randomized studies on human subjects are needed to evaluate the potential advantages of the proposed diagnostic parameters for longitudinal assessment of AVF functionality.

CONCLUSION

According to KDOQI guidelines, a blood flow (Q_a) < 400-500 mL/min and a ratio of venous access pressure to main arterial pressure (VAPR) > 0.55 are associated with the existence of a significant stenosis which needs immediate interventional care. However, an AVF can maintain a relatively high blood flow rate and a normal VAPR despite the presence of a significant stenosis. The Q_a has shown to be a strong predictor of an inflow stenosis, whereas VAPR has shown to be a poor predictor of stenotic lesions in AVFs. These shortcomings have been mainly attributed to the fact that under a developing stenosis both pressure and flow profiles change, and thus, relying on only one of these parameters to detect a significant stenosis could be inadequate. Similar shortcomings also have been reported in detection of coronary and renal stenosis based on diagnostic endpoints that are either based on flow or pressure. In the context of coronary or renal stenosis, it has been shown that the diagnostic endpoints that combine the effects of pressure and flow can better predict the functional severity of a stenosis. This similarity inspired us to bridge between the advances in diagnostic field of coronary and renal stenosis with the diagnosis of stenotic lesions in AVFs. The new functional diagnostic endpoints are based on fundamental fluid dynamics concepts and are primarily presented in two major forms including: (1) resistance index (a ratio of pressure drop by flow); and (2) pressure drop coefficient (the pressure drop normalized by the dynamic pressure). We believe that these endpoints are capable of better distinguishing changes in the hemodynamic variations (pressure and flow) and thus, could be promising diagnostic tools to detect the functional severity of stenosis in AVFs.

REFERENCES

1 **Howard AD**, Howard RS, Goldstein SL, Meyer KB. Fistula First Breakthrough Initiative (FFBI): lessons about arteriovenous fistula prevalence goals. *Am J Kidney Dis* 2013; **61**: 523-525 [PMID: 23157938 DOI: 10.1053/j.ajkd.2012.09.014]

2 **Dember LM**, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, Himmelfarb J, Vazquez MA, Gassman JJ, Greene T, Radeva MK, Braden GL, Ikizler TA, Rocco MV, Davidson IJ, Kaufman JS, Meyers CM, Kusek JW, Feldman HI. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA* 2008; **299**: 2164-2171 [PMID: 18477783 DOI: 10.1001/jama.299.18.2164]

3 **Sehgal AR**, Snow RJ, Singer ME, Amini SB, DeOreo PB, Silver MR, Cebul RD. Barriers to adequate delivery of hemodialysis. *Am J Kidney Dis* 1998; **31**: 593-601 [PMID: 9531174]

4 **Allon M**, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney Int* 2002; **62**: 1109-1124 [PMID: 12234281 DOI: 10.1111/j.1523-1755.2002.kid551.x]

5 **Gallieni M**, Martini A, Mezzina N. Dialysis access: an increasingly important clinical issue. *Int J Artif Organs* 2009; **32**: 851-856 [PMID: 20037889]

6 **Lok CE**, Bhola C, Croxford R, Richardson RM. Reducing vascular access morbidity: a comparative trial of two vascular access monitoring strategies. *Nephrol Dial Transplant* 2003; **18**: 1174-1180 [PMID: 12748352]

7 **Scaffaro LA**, Bettio JA, Cavazzola SA, Campos BT, Burmeister JE, Pereira RM, Barcellos CS, Caramori P. Maintenance of hemodialysis arteriovenous fistulas by an interventional strategy: clinical and duplex ultrasonographic surveillance followed by transluminal angioplasty. *J Ultrasound Med* 2009; **28**: 1159-1165 [PMID: 19710213]

8 **Campos RP**, Do Nascimento MM, Chula DC, Do Nascimento DE, Riella MC. Stenosis in hemodialysis arteriovenous fistula: evaluation and treatment. *Hemodial Int* 2006; **10**: 152-161 [PMID: 16623667 DOI: 10.1111/j.1542-4758.2006.00087.x]

9 **Feddersen MA**, Roger SD. Arteriovenous fistula surveillance: everyone's responsibility. *Port J Nephrol Hypert* 2012; **26**: 255-265

10 **Kumbar L**, Karim J, Besarab A. Surveillance and monitoring of dialysis access. *Int J Nephrol* 2012; **2012**: 649735 [PMID: 22164333 DOI: 10.1155/2012/649735]

11 NKF-DOQI clinical practice guidelines for vascular access. National Kidney Foundation-Dialysis Outcomes Quality Initiative. *Am J Kidney Dis* 1997; **30**: S150-S191 [PMID: 9339150]

12 **Vascular Access Work Group**. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; **48** Suppl 1: S248-S273 [PMID: 16813991 DOI: 10.1053/j.ajkd.2006.04.040]

13 **Vachharajani TJ**. Diagnosis of arteriovenous fistula dysfunction. *Semin Dial* 2012; **25**: 445-450 [PMID: 22694731 DOI: 10.1111/j.1525-139X.2012.01094.x]

14 **Paulson WD**, Work J. Controversial vascular access surveillance mandate. *Semin Dial* 2010; **23**: 92-94 [PMID: 20331824 DOI: 10.1111/j.1525-139X.2009.00682.x]

15 **Polkinghorne KR**, Lau KK, Saunder A, Atkins RC, Kerr PG. Does monthly native arteriovenous fistula blood-flow surveillance detect significant stenosis--a randomized controlled trial. *Nephrol Dial Transplant* 2006; **21**: 2498-2506 [PMID: 16854848 DOI: 10.1093/ndt/gfl242]

16 **Shetty A**, Whittier WL. Does regular surveillance improve the long-term survival of arteriovenous fistulas? *Int J Nephrol* 2012; **2012**: 539608 [PMID: 22187644 DOI: 10.1155/2012/539608]

17 **Sands JJ**. Vascular access monitoring improves outcomes. *Blood Purif* 2005; **23**: 45-49 [PMID: 15627736]

18 **Paulson WD**, Moist L, Lok CE. Vascular access surveillance: an ongoing controversy. *Kidney Int* 2012; **81**: 132-142 [PMID: 21975864 DOI: 10.1038/ki.2011.337]

19 **Smith GE**, Gohil R, Chetter IC. Factors affecting the patency of arteriovenous fistulas for dialysis access. *J Vasc Surg* 2012; **55**: 849-855 [PMID: 22070937 DOI: 10.1016/j.jvs.2011.07.095]

20 **Christou MA**, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. *Am J Cardiol* 2007; **99**: 450-456 [PMID: 17293182 DOI: 10.1016/j.amjcard.2006.09.092]

21 **Hoffman JI**. Problems of coronary flow reserve. *Ann Biomed Eng* 2000; **28**: 884-896 [PMID: 11144672 DOI: 10.1114/1.1308503]

22 **Kushner FG**, Hand M, Smith SC, King SB, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2009; **54**: 2205-2241 [PMID: 19942100 DOI: 10.1016/j.jacc.2009.10.015]

23 **Pijls NH**, Kern MJ, Yock PG, De Bruyne B. Practice and potential pitfalls of coronary pressure measurement. *Catheter Cardiovasc Interv* 2000; **49**: 1-16 [PMID: 10627357 DOI: 10.1002/(sici)1522-726x(200001)49:1<1::aid-ccd1>3.0.co;2-5]

24 **Roy AS**, Banerjee RK, Back LH, Back MR, Khoury S, Millard RW. Delineating the guidewire flow obstruction effect in assessment of fractional flow reserve and coronary flow reserve measurements. *Am J Physiol Heart Circ Physiol* 2005; **289**: H392-H397 [PMID: 15734887 DOI: 10.1152/ajpheart.00798.2004]

25 **Asif A**, Gadalean FN, Merrill D, Cherla G, Cipleu CD, Epstein DL, Roth D. Inflow stenosis in arteriovenous fistulas and grafts: a multicenter, prospective study. *Kidney Int* 2005; **67**: 1986-1992 [PMID: 15840048 DOI: 10.1111/j.1523-1755.2005.00299.x]

26 **White JJ**, Ram SJ, Jones SA, Schwab SJ, Paulson WD. Influence of luminal diameters on flow surveillance of hemodialysis grafts: insights from a mathematical model. *Clin J Am Soc Nephrol* 2006; **1**: 972-978 [PMID: 17699315 DOI: 10.2215/cjn.00580206]

27 **Fahrtash F**, Kairaitis L, Gruenewald S, Spicer T, Sidrak H, Fletcher J, Allen R, Swinnen J. Defining a significant stenosis in an autologous radio-cephalic arteriovenous fistula for hemodialysis. *Semin Dial* 2011; **24**: 231-238 [PMID: 21517992 DOI: 10.1111/j.1525-139X.2011.00861.x]

28 **Tuka V**, Malik J. Vascular access surveillance: no benefit? *Am J Kidney Dis* 2008; **52**: 628; author reply 628-629 [PMID: 18725022 DOI: 10.1053/j.ajkd.2008.05.035]

29 **Campos RP**, Chula DC, Perreto S, Riella MC, do Nascimento MM. Accuracy of physical examination and intra-access pressure in the detection of stenosis in hemodialysis arteriovenous fistula. *Semin Dial* 2008; **21**: 269-273 [PMID: 18248519 DOI: 10.1111/j.1525-139X.2007.00419.x]

30 **Tessitore N**, Bedogna V, Verlato G, Poli A. The rise and fall of access blood flow surveillance in arteriovenous fistulas. *Semin Dial* 2014; **27**: 108-118 [PMID: 24494667 DOI: 10.1111/sdi.12187]

31 **Mercadal L**, Challier E, Cluzel P, Hamani A, Boulechfar H, Boukhalfa Z, Izzedine H, Bassilios N, Barrou B, Deray G, Petitclerc T. Detection of vascular access stenosis by measurement of access blood flow from ionic dialysance. *Blood Purif* 2002; **20**: 177-181 [PMID: 11818682]

32 **Tessitore N**, Bedogna V, Gammaro L, Lipari G, Poli A, Baggio E, Firpo M, Morana G, Mansueto G, Maschio G. Diagnostic accuracy of ultrasound dilution access blood flow measurement in detecting stenosis and predicting thrombosis in native forearm arteriovenous fistulae for hemodialysis. *Am J Kidney Dis* 2003; **42**: 331-341 [PMID: 12900816 DOI: 10.1016/S0272-6386(03)00659-0]

33 **Tessitore N**, Bedogna V, Melilli E, Millardi D, Mansueto G, Lipari G, Mantovani W, Baggio E, Poli A, Lupo A. In search of an optimal bedside screening program for arteriovenous fistula stenosis. *Clin J Am Soc Nephrol* 2011; **6**: 819-826 [PMID: 21454718 DOI: 10.2215/CJN.06220710]

34 **Tonelli M**, Jhangri GS, Hirsch DJ, Marryatt J, Mossop P, Wile C, Jindal KK. Best threshold for diagnosis of stenosis or thrombosis within six months of access flow measurement in arteriovenous fistulae. *J Am Soc Nephrol* 2003; **14**: 3264-3269 [PMID: 14638925 DOI: 10.1097/01.asn.0000099381.98940.2e]

35 **Schwarz C**, Mitterbauer C, Boczula M, Maca T, Funovics M, Heinze G, Lorenz M, Kovarik J, Oberbauer R. Flow monitoring: performance characteristics of ultrasound dilution versus color Doppler ultrasound compared with fistulography. *Am J Kidney Dis* 2003; **42**: 539-545 [PMID: 12955682 DOI: 10.1016/S0272-6386(03)00786-8]

36 **Tessitore N**, Bedogna V, Poli A, Lipari G, Pertile P, Baggio E, Contro A, Criscenti P, Mansueto G, Lupo A. Should current criteria for detecting and repairing arteriovenous fistula stenosis be reconsidered? Interim analysis of a randomized controlled trial. *Nephrol Dial Transplant* 2014; **29**: 179-187 [PMID: 24166470 DOI: 10.1093/ndt/gft421]

37 **Besarab A**, al-Saghir F, Alnabhan N, Lubkowski T, Frinak S.

Simplified measurement of intra-access pressure. *ASAIO J* 1996; **42**: M682-M687 [PMID: 8944967]
38 **Besarab A**, Frinak S, Sherman RA, Goldman J, Dumler F, Devita MV, Kapoian T, Al-Saghir F, Lubkowski T. Simplified measurement of intra-access pressure. *J Am Soc Nephrol* 1998; **9**: 284-289 [PMID: 9527405]
39 **Besarab A**, Lubkowski T, Frinak S, Ramanathan S, Escobar F. Detecting vascular access dysfunction. *ASAIO J* 1997; **43**: M539-M543 [PMID: 9360101]
40 **Smits JH**, van der Linden J, Hagen EC, Modderkolk-Cammeraat EC, Feith GW, Koomans HA, van den Dorpel MA, Blankestijn PJ. Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int* 2001; **59**: 1551-1558 [PMID: 11260420 DOI: 10.1046/j.1523-1755.2001.0590041551.x]
41 **Feldman HI**, Joffe M, Rosas SE, Burns JE, Knauss J, Brayman K. Predictors of successful arteriovenous fistula maturation. *Am J Kidney Dis* 2003; **42**: 1000-1012 [PMID: 14582044]
42 **Lauvao LS**, Ihnat DM, Goshima KR, Chavez L, Gruessner AC, Mills JL. Vein diameter is the major predictor of fistula maturation. *J Vasc Surg* 2009; **49**: 1499-1504 [PMID: 19497513 DOI: 10.1016/j.jvs.2009.02.018]
43 **Mendes RR**, Farber MA, Marston WA, Dinwiddie LC, Keagy BA, Burnham SJ. Prediction of wrist arteriovenous fistula maturation with preoperative vein mapping with ultrasonography. *J Vasc Surg* 2002; **36**: 460-463 [PMID: 12218967 DOI: 10.1067/mva.2002.126544]
44 **Wong V**, Ward R, Taylor J, Selvakumar S, How TV, Bakran A. Reprinted article "Factors associated with early failure of arteriovenous fistulae for haemodialysis access". *Eur J Vasc Endovasc Surg* 2011; **42** Suppl 1: S48-S54 [PMID: 21855022 DOI: 10.1016/j.ejvs.2011.06.023]
45 **Malik J**, Tuka V, Tesar V. Local hemodynamics of the vascular access for hemodialysis. *Kidney Blood Press Res* 2009; **32**: 59-66 [PMID: 19258724 DOI: 10.1159/000205522]
46 **Roy-Chaudhury P**, Arend L, Zhang J, Krishnamoorthy M, Wang Y, Banerjee R, Samaha A, Munda R. Neointimal hyperplasia in early arteriovenous fistula failure. *Am J Kidney Dis* 2007; **50**: 782-790 [PMID: 17954291 DOI: 10.1053/j.ajkd.2007.07.019]
47 **Roy-Chaudhury P**, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol* 2006; **17**: 1112-1127 [PMID: 16565259 DOI: 10.1681/ASN.2005050615]
48 **Vita JA**, Holbrook M, Palmisano J, Shenouda SM, Chung WB, Hamburg NM, Eskenazi BR, Joseph L, Shapira OM. Flow-induced arterial remodeling relates to endothelial function in the human forearm. *Circulation* 2008; **117**: 3126-3133 [PMID: 18541736 DOI: 10.1161/CIRCULATIONAHA.108.778472]
49 **London GM**, Marchais SJ, Guerin AP, Metivier F, Adda H. Arterial structure and function in end-stage renal disease. *Nephrol Dial Transplant* 2002; **17**: 1713-1724 [PMID: 12270974 DOI: 10.1093/ndt/17.10.1713]
50 **Rajabi-Jagahrgh E**, Krishnamoorthy MK, Roy-Chaudhury P, Succop P, Wang Y, Choe A, Banerjee RK. Longitudinal assessment of hemodynamic endpoints in predicting arteriovenous fistula maturation. *Semin Dial* 2012; **26**: 208-215 [PMID: 22892020 DOI: 10.1111/j.1525-139X]
51 **Rajabi-Jagahrgh E**, Krishnamoorthy MK, Wang Y, Choe A, Roy-Chaudhury P, Banerjee RK. Influence of temporal variation in wall shear stress on intima-media thickening in arteriovenous fistulae. *Semin Dial* 2012; **26**: 511-519 [PMID: 23278290 DOI: 10.1111/sdi.12045]
52 **Banerjee RK**, Sinha Roy A, Back LH, Back MR, Khoury SF, Millard RW. Characterizing momentum change and viscous loss of a hemodynamic endpoint in assessment of coronary lesions. *J Biomech* 2007; **40**: 652-662 [PMID: 16530204 DOI: 10.1016/j.jbiomech.2006.01.014]
53 **Siebes M**, Verhoeff BJ, Meuwissen M, de Winter RJ, Spaan JA, Piek JJ. Single-wire pressure and flow velocity measurement to quantify coronary stenosis hemodynamics and effects of percutaneous interventions. *Circulation* 2004; **109**: 756-762 [PMID: 14970112 DOI: 10.1161/01.CIR.0000112571.06979.B2]
54 **Sinha Roy A**, Back LH, Banerjee RK. Guidewire flow obstruction effect on pressure drop-flow relationship in moderate coronary artery stenosis. *J Biomech* 2006; **39**: 853-864 [PMID: 16488224 DOI: 10.1016/j.jbiomech.2005.01.020]
55 **Chamuleau SA**, Siebes M, Meuwissen M, Koch KT, Spaan JA, Piek JJ. Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. *Am J Physiol Heart Circ Physiol* 2003; **285**: H2194-H2200 [PMID: 12829432]
56 **Spaan JA**, Piek JJ, Hoffman JI, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. *Circulation* 2006; **113**: 446-455 [PMID: 16432075 DOI: 10.1161/circulationaha.105.587196]
57 **Tamita K**, Akasaka T, Takagi T, Yamamuro A, Yamabe K, Katayama M, Morioka S, Yoshida K. Effects of microvascular dysfunction on myocardial fractional flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction. *Catheter Cardiovasc Interv* 2002; **57**: 452-459 [PMID: 12455078 DOI: 10.1002/ccd.10350]
58 **De Bruyne B**, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, Gould KL, Wijns W. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation* 2001; **104**: 2401-2406 [PMID: 11705815 DOI: 10.1161/hc4501.099316]
59 **Pijls NH**. Is it time to measure fractional flow reserve in all patients? *J Am Coll Cardiol* 2003; **41**: 1122-1124 [PMID: 12679211 DOI: 10.1016/s0735-1097(03)00056-1]
60 **Peelukhana SV**, Back LH, Banerjee RK. Influence of coronary collateral flow on coronary diagnostic parameters: an in vitro study. *J Biomech* 2009; **42**: 2753-2759 [PMID: 19775695 DOI: 10.1016/j.jbiomech.2009.08.013]
61 **Meuwissen M**, Siebes M, Chamuleau SA, van Eck-Smit BL, Koch KT, de Winter RJ, Tijssen JG, Spaan JA, Piek JJ. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. *Circulation* 2002; **106**: 441-446 [PMID: 12135943 DOI: 10.1161/01.cir.0000023041.26199.29]
62 **Ng MK**, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. *Circulation* 2006; **113**: 2054-2061 [PMID: 16636168 DOI: 10.1161/circulationaha.105.603522]
63 **Sinha Roy A**, Back MR, Khoury SF, Schneeberger EW, Back LH, Velury VV, Millard RW, Banerjee RK. Functional and anatomical diagnosis of coronary artery stenoses. *J Surg Res* 2008; **150**: 24-33 [PMID: 18262546 DOI: 10.1016/j.jss.2007.10.018]
64 **Kolli KK**, Banerjee RK, Peelukhana SV, Helmy TA, Leesar MA, Arif I, Schneeberger EW, Hand D, Succop P, Gottliebson WM, Effat MA. Influence of heart rate on fractional flow reserve, pressure drop coefficient, and lesion flow coefficient for epicardial coronary stenosis in a porcine model. *Am J Physiol Heart Circ Physiol* 2011; **300**: H382-H387 [PMID: 20935151 DOI: 10.1152/ajpheart.00412.2010]
65 **Rajabi-Jaghargh E**, Kolli KK, Back LH, Banerjee RK. Effect of guidewire on contribution of loss due to momentum change and viscous loss to the translesional pressure drop across coronary artery stenosis: an analytical approach. *Biomed Eng Online* 2011; **10**: 51 [PMID: 21658283 DOI: 10.1186/1475-925X-10-51]
66 **Kolli KK**, Helmy TA, Peelukhana SV, Arif I, Leesar MA, Back LH, Banerjee RK, Effat MA. Functional diagnosis of coronary stenoses using pressure drop coefficient: a pilot study in humans. *Catheter Cardiovasc Interv* 2014; **83**: 377-385 [PMID: 23785016 DOI: 10.1002/ccd.25085]
67 **Kolli KK**, Arif I, Peelukhana SV, Succop P, Back LH, Helmy TA, Leesar MA, Effat MA, Banerjee RK. Diagnostic performance of pressure drop coefficient in relation to fractional flow reserve and coronary flow reserve. *J Invasive Cardiol* 2014; **26**: 188-195 [PMID: 24791716]
68 **Kolli KK**, Effat MA, Peelukhana SV, Succop P, Back LH,

Leesar MA, Helmy TA, Imran A, Banerjee RK. Hyperemia-free delineation of epicardial and microvascular impairments using a basal index. *Ann Biomed Eng* 2014; **42**: 1681-1690 [PMID: 24806315 DOI: 10.1007/s10439-014-1020-x]

69 **van de Hoef TP**, van Lavieren MA, Damman P, Delewi R, Piek MA, Chamuleau SA, Voskuil M, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Meuwissen M, Piek JJ. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv* 2014; **7**: 301-311 [PMID: 24782198 DOI: 10.1161/CIRCINTERVENTIONS.113.001049]

70 **Rajabi-Jaghargh E**, Banerjee RK. Functional Diagnostic Parameters for Arteriovenous Fistula. *Artificial Organs* 2014; In press

P- Reviewer: Pan HC, Stolic RV **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

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