SHORT COMMUNICATION

Systemic microvascular endothelial function with arteriovenous fistula creation in chronic kidney disease

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Background: This study aimed to determine changes in microvascular endothelial function with upper arm arteriovenous fistula (AVF) creation and maturation in patients with chronic kidney disease (CKD). **Materials and Methods:** This prospective cross-sectional study was performed at Hospital Universiti Sains Malaysia, a tertiary hospital in Malaysia. Forty CKD patients (stage 4–5) who were scheduled for elective AVF creation over the upper extremity for maintenance hemodialysis were recruited using convenience sampling method. Microvascular endothelial-dependent vasodilation was measured using laser Doppler flowmetry and the process of iontophoresis preoperatively and postoperatively at weeks 2 and 6. Fistula maturation was assessed at week 6. **Results:** Thirty-two patients had successful AVF maturation. Endothelial-dependent vasodilation (acetylcholine (Ach)%) was higher (246.48 [standard deviation (SD) 209.38] vs. 104.95 [SD 43.29], $P = 0.001$) while systolic blood pressure was lower (142.25 [SD 21.50] vs. 162.25 [SD 13.26], $P = 0.017$) in this group as compared to unsuccessful AVF group. No significant changes were seen in overall microvascular endothelial-dependent vasodilation during the 6-week study period (day 0, 246.48 [SD 209.38]; week 2, 201.14 [SD 198.19]; and week 6, 203.53 [SD 145.89]). **Conclusion:** Upper arm AVF creation does not affect microvascular endothelial function up to 6 weeks post operation and may not contribute to the success of AVF maturation. However, the lower microvascular endothelial-dependent vasodilation and higher systolic blood pressure in unsuccessful AVF subjects need to be further studied.

Key words: Arteriovenous fistula, chronic kidney disease, hemodialysis, microcirculation, vascular access

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INTRODUCTION

Upper extremity native arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis as it offers higher blood flow, longer access survival, and less likelihood for complications.[1]

Although the use of AVF has delivered clinically positive impact, there is inadequate information regarding the changes in systemic microvascular endothelial function that occurs due to the AVF creation and maturation. A recent study reported that in patients who had successful AVF creation, both distal and proximal skin hand perfusion was not different between the operated and control limbs before and after AVF creation and maturation.[2] However, these findings were based on direct *in situ* measurement of skin perfusion and did not reflect the changes in microvascular endothelial function in relation to AVF creation and maturation. Endothelial cells line the inner lumen of blood vessels.

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They release substances that affect vascular tone and maintain the vascular homeostasis and health. Dysfunction of endothelial cells, termed endothelial dysfunction, might be involved in the occurrence of complications due to AVF creation in patients with chronic kidney disease (CKD).[3] Therefore, it is important to investigate whether changes in microvascular endothelial function occur in relation to AVF creation and maturation as this could be useful to identify and prevent the potential complications that may occur as a result of AVF creation.

MATERIALS AND METHODS

Study design and setting

This prospective cross-sectional study was conducted at Hospital Universiti Sains Malaysia (HUSM) with 2-year study duration. The procedures of this study have been approved by the Research Ethics Committee (human) of Universiti Sains Malaysia (USM/JEPeM/140394), and conducted according to the principles of the Declaration of Helsinki. All patients received detailed information about the study procedures and provided written informed consent prior to any study procedures. Demographic, anthropometry, blood pressure, and medical history were obtained before AVF creation while microvascular endothelial function was measured before AVF creation and postoperatively at weeks 2 and 6.

Patients

Forty patients with CKD stages 4 and 5, clinically stable, and aged more than 18 years old scheduled for elective AVF creation over the upper extremity at HUSM were included in this study based on convenience sampling method. Forty patients were recruited based on sample size calculation using PS power and sample size calculations version 3.0 software. With level of significance (α) set at 0.05, power (0.80), expected different in endothelium-dependent vasodilatation (11.6 arbitrary units), standard deviation (SD) (σ) at 23.71,[4] and after considering 10% dropout, a minimum of 39 patients were required. Patients were identified from scheduled AVF creation list at the Universiti Sains Malaysia Hospital. Patients with symptomatic peripheral vascular disease or ankle-brachial systolic index < 0.4, preexisting central vein stenosis, vasculitis, dermatological diseases involving the upper extremities, and on nonsteroidal anti-inflammatory drugs and beta-2 adrenergic receptor agonists were excluded from this study. Six weeks after the AVF creation, patients were assessed for AVF maturation and divided into successful or unsuccessful AVF groups.

Arteriovenous fistula

The fistula type, either radial or brachial cephalic fistula, was chosen regarding the vessel suitability (diameter of vein and artery, distensibility of vein, and pulsation of artery) based on clinical examination and preoperative Doppler ultrasound. Fistula maturation was described as a process by which a fistula becomes suitable for cannulation and was assessed at week 6. A fistula was considered to reach successful maturation when it meets a diameter of at least 0.6 cm with discernible margins when a tourniquet is in place, flows throughout venous limb at >600 ml/min, and is located at no more than 0.6 cm from the skin surface.[1]

Demographic and medical history

Demographic data and medical history of participating patients were obtained from interview session and from the medical records. Diagnosed comorbidities such as diabetes, hypertension, hyperlipidemia, and heart disease were recorded.

Anthropometry and blood pressure measurements

Body weight and height were measured using a digital weight scale with an attached height rod scale (Seca, Hamburg, Germany). Body mass index (BMI) was calculated as the ratio of weight (kg) to height (m^2) (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure, as well as heart rate, were measured in the sitting position using digital blood pressure monitor (Omron, Japan) after at least 10 min of rest. Two readings were taken 5 min apart, and the mean reading was recorded.

Assessment of microvascular endothelial function

The microvascular endothelial function was measured using laser Doppler flowmetry (LDF) and the process of iontophoresis preoperatively (before AVF creation) and postoperatively at weeks 2 and 6. Patients were asked not to perform heavy exercise a day before measurement and refrained from consuming caffeine-containing drinks, high-salt diet, and smoking for at least 12 h prior. During the study period, no acute illnesses or major complications were reported and there was no documented change on medication of our subjects before and after operation.

Microvascular endothelial function which consists of microvascular endothelial-dependent and microvascular endothelial-independent vasodilation assessments was measured noninvasively using LDF and the process of iontophoresis; the procedures and reproducibility had been reported previously by our team.[5] All procedures were carried out between 8 am and 12 pm in a specific quiet, temperature-monitored (24°C ± 1°C) experimental room by a single operator. Patients were allowed to familiarize with the room condition in a supine condition for at least 10 min before any measurements were performed. Microvascular endothelial function was measured in supine position, where the forearm of operated upper limb was placed at the side of body and stabilized with a

special hand supporter (to limit unintentional movements). To ensure that LDF readings were taken from consistent areas and standardized in all patients, the SNP chamber (filled with sodium nitroprusside, SNP) was placed 5 cm from the wrist crease and the ACh chamber (filled with acetylcholine, ACh) was placed 5 cm apart from the SNP chamber. The continuous real-time local cutaneous skin perfusion of the operated forearm was measured using dual-channel DRT4 LDF (Moor Instruments, Axminster, UK) with the DP1T-V2 skin laser probes (Moor Instruments, Axminster, UK). Probe one and two were attached to ACh and SNP chamber, respectively. Changes in microvascular perfusion were captured by the MoorSoft for Windows/ DRT4 software package version 1.2 (Moor Instruments, Axminster, United Kingdom). Iontophoresis is a method of delivering ionic drugs into the skin by applying a low voltage to a drug solution. Iontophoresis of freshly prepared 1% acetylcholine, ACh (Fluka Chemie Gmbh, Buchs, Switzerland) and iontophoresis of 1% sodium nitroprusside, SNP (Riedel-de Haen, Seelze, Germany) in 0.9% sodium chloride (Excel Pharmaceutical, Selangor, Malaysia) were used to assess endothelial-dependent and endothelial-independent vasodilations, respectively. Ach- and SNP-induced vasodilations were quantified as percent change in perfusion in response to ACh (ACh %) and SNP (SNP %) and were calculated using this formula: maximum change/minimum baseline × 100.[5]

Statistical analysis

Statistical analyses were performed using the IBM® SPSS® Statistics version 22 software for Windows (IBM®, Armonk, New York, United States). Data exploration was performed to identify missing values. The software was set to perform listwise deletion, where a case is dropped from an analysis due to a missing value in at least one of the specified variables. Only cases with a complete set of data were analyzed. Results were expressed as mean (SD) while categorical data were expressed as frequency (percentage). Between-group mean differences of studied parameters were analyzed using independent *t*-test, while for categorical data, Chi-square test was used. Repeated measures ANOVA (RMA) was used to analyze the changes in microvascular endothelial function for each (successful and unsuccessful AVF) group during the study period (baseline and 2 and 6 weeks postoperatively). RMA was also applied to analyze the changes in microvascular endothelial function between the successful and unsuccessful AVF groups at the baseline and 2 and 6 weeks postoperatively. Statistical significance was set at alpha = 0.05.

RESULTS

Forty patients underwent either radial (20 patients) or brachial (20 patients) types of AVF creation operation. Thirty-two patients showed successful AVF maturation while 8 patients did not have a successful AVF maturation at week 6 postoperative. The mean age for all patients was 55.98 (SD 9.97) years consisting of 52.5% and 47.5% of male and female patients, respectively. Three or 7.5% of patients were stage 4 CKD while the rest were stage 5. Seventy percent (95% confidence interval [CI]: 0.54, 0.83) of patients had diabetes, 95% (95% CI: 0.83, 0.99) had hypertension, 52% (95% CI: 0.36, 0.69) had hyperlipidemia, only 1% (95% CI: 0.87, 0.99) had heart disease, and 65% (95% CI: 0.48, 0.79) had both diabetes and hypertension. Microvascular endothelial function, BMI, and SBP were significantly different between the successful and unsuccessful AVF groups, where patients with successful AVF have better microvascular endothelial function values at baseline (preoperatively), as indicated by a higher percent change to acetylcholine (ACh%) compared to the unsuccessful group (P = 0.001) [Table 1]. BMI was significantly higher (P = 0.027) while SBP was significantly lower (P = 0.017) in the successful AVF group.

The changes in ACh% and SNP% from baseline to week 2 and week 6 in the successful and unsuccessful AVF groups are shown in Table 2. Analysis by RMA using 3-point measurements at baseline and 2 and 6 weeks did not show a significant overall change in ACh% and SNP% from baseline to week 6 in each group. For time-group interaction analysis, the changes of ACh% and SNP% were found not to be significantly different between both the groups throughout the study period (ACh%, P = 0.646; SNP%, P = 0.940).

DISCUSSION

In the successful upper-limb AVF creation, we found that measurements of microvascular endothelial function did not change significantly from baseline (before the AVF creation) and up to 6 weeks after the AVF creation. However, subjects with successful AVF creation had higher baseline microvascular endothelial function compared to unsuccessful subjects. A previous study revealed that patients with successful AVF formation have significantly reduced endothelial-dependent vasodilation after 2 weeks of AVF creation;[6] their percent reduction was 36% compared to our study of 18.4%. However, the longer duration of our study follow-up till maturation at 6 weeks post AVF creation showed that microvascular endothelial-dependent vasodilation did not change compared to week 2 post AVF creation. That study[6] also reported the insignificant change in microvascular endothelial-independent vasodilation postoperatively after AVF creation, which is similar to our study.

It was hypothesized that AVF remodeling as measured by intraoperative arterial and venous luminal dilation was an endothelium-dependent process, and showed a positive

Table 1: Demographic and cardiovascular risk factors of patients (*n*=40)

Parameters	Unsuccessful AVF (*n*=8)	Successful AVF (*n*=32)	*P*
Age (years)[a]	57.63±7.56	55.56±10.55	0.607
Gender (male: female)[b]	1 (12.5):7 (87.5)	20 (62.5): 12 (37.5)	0.011*
CKD stage (4:5)[b]	1 (12.5):7 (87.5)	2 (6):30 (94)	0.548
Fistula type (radial: brachial)[b]	7 (87.5):1 (12.5)	13 (40.6): 19 (59.4)	0.018*
Diabetes (%)[b]	8 (100)	20 (63)	0.038*
Hypertension (%)[b]	8 (100)	30 (94)	0.468
Hyperlipidemia (%)[b]	5 (63)	16 (50)	0.527
Heart disease (%)[b]	0 (0)	1 (3)	0.613
Diabetes with hypertension (%)[b]	8 (100)	18 (56)	0.020*
Body weight (kg)[a]	57.84±6.62	65.33±12.03	0.100
BMI (kg/m^2)[a]	23.98±1.47	26.30±4.88	0.027†
Systolic BP (mmHg)[a]	162.25±13.26	142.25±21.50	0.017†
Diastolic BP (mmHg)[a]	74.88±7.36	78.41±12.61	0.454
Heart rate (rate/min)[a]	70.13±9.01	76.25±9.96	0.122
ACh%[a]	104.95±43.29	246.48±209.38	0.001†
SNP%[a]	213.01±217.28	304.66±279.65	0.395

*P<0.05, Chi-Square test, †P<0.05, Independent t-test, [a]Data presented as mean±SD, [b]Data presented as frequency (%). CKD=Chronic kidney disease; BMI=Body mass index; BP=Blood pressure; ACh %=Acetylcholine percent change; SNP %=Sodium nitroprusside percent change; AVF=Arteriovenous fistula; SD=Standard deviation

Table 2: Microvascular endothelial-dependent (acetylcholine percent change) and microvascular endothelial-independent (sodium nitroprusside percent change) vasodilation in successful and unsuccessful arteriovenous fistula group

Parameters	Mean±SD (*n*=32)			*P*
	Day 0	Week 2	Week 6	
Successful AVF group				
ACh%	246.48±209.38	201.14±198.19	203.53±145.89	0.523
SNP%	304.56±279.65	261.97±237.59	324.41±381.60	0.716
Unsuccessful AVF group				
ACh%	104.95±43.29	132.49±158.83	91.87±38.37	0.612
SNP%	213.01±217.28	130.32±95.35	247.60±135.72	0.347

Data presented as mean±SD. RMA. ACh%=Acetylcholine percent change; SNP%=Sodium nitroprusside percent change; AVF=Arteriovenous fistula; SD=Standard deviation; RMA=Repeated measures ANOVA

correlation between brachial artery endothelial function as measured by flow-mediated dilation with increased percent of arterial and venous luminal diameter.[7] Venous dilation is expected to occur in order to normalize the wall shear stress (WSS) that rises due to increased blood delivery through the venous outflow limb of AVF.

AVF creation can create unstable blood flow at the local circulation. Unstable blood flow, together with the changes in shear stress, has been shown to be associated with increased endothelial cell turnover at the lesion-prone region.[8] Besides unstable flow, transitional flow was also reported to cause changes in endothelial cell shape and loss of endothelial cell alignment due to fluctuating shear stress.[9] It is possible that the process of vascular remodeling might contribute to the improvement in microvascular endothelial function towards the AVF maturation, where there were sufficient blood flow and normalized WSS that occur in conjunction with AVF maturation and improve endothelial cell functioning. However, our study was not able to show these changes.

Our study showed the significant difference in gender, type of fistula, SBP, ACh%, and the existence of comorbidities such as diabetes and hypertension between the successful and unsuccessful AVF groups. The association of gender, type of fistula, existence of diabetes, and hypertension with the success or failure of AVF maturation in CKD patients has been reported before.[10-13] Female patients and the presence of diabetes and hypertension showed a significant association with the failure of AVF. Compared to brachial artery, anastomosis based on radial artery demonstrated higher odds of early thrombosis that contributes to AVF failure.[11] Meanwhile, SBP above 122.5 mmHg has improved the AVF maturation time.[14] However, a previous study had reported that obesity (BMI <30 kg/m^2 as reference) was not a factor affecting the failure of AVF maturity;[15] the association only appeared in the highest category of BMI (≥35°kg/m^2).[15] The mean BMI in the present study was 25.84 (SD 4.49) kg/m^2, and only two patients were classified in BMI ≥ 35 kg/m^2 category. The majority of our patients were classified in the category of BMI <25 (n = 18) and BMI 25–29.9 (n = 15) kg/m^2 categories.

Majority of the patients had diabetes or hypertension. This is understandable since diabetes and hypertension are closely related to CKD while other factors such as diet and Vitamin D deficiency contribute to the increased risk of CKD in diabetic patients.[16,17] The relatively small sample size of 40 patients, which is similar to the previous study (n = 43),[6] may reduce the power in statistical tests to detect the difference in microvascular endothelial function before and after the AVF creation. Despite the small sample size, a difference was seen between the successful and unsuccessful groups, in the preoperative microvascular endothelial function and SBP, where better microvascular endothelial function and markedly lower SBP were seen in the successful group. Because of the small and imbalanced sample size between the two groups, these observations do not allow us to explore the possible causal role between microvascular endothelial function and successful AVF maturation. These interesting observations need to be confirmed with another study using adequate sample size, specifically to assess these parameters. However, this study provides new preliminary data on the pattern of changes in microvascular endothelial-dependent and microvascular endothelial-independent vasodilatations preoperatively and for a period up to AVF maturation, 6 weeks after AVF creation.

CONCLUSION

In successful upper-limb AVF creation, measurements of microvascular endothelial function did not change significantly from baseline (before AVF creation) and up to 6 weeks after the AVF creation. Thus, AVF creation does not appear to affect systemic microvascular endothelial function throughout the 6-week study period. Before AVF creation, subjects with successful AVF creation had better microvascular endothelial-dependent vasodilation and significantly lower systolic blood pressure than those who failed. A larger study is needed to confirm the impact of these factors on the success of AVF creation.

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Conflicts of interest

There are no conflicts of interest.

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