Effect of Inflow Arterial Calcification on Arteriovenous Fistula Maturation

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Background: The aim of this study is to investigate the effect of preexisting calcification in the inflow artery on maturation and flow volume of an arteriovenous fistula (AVF).
Methods: Patients who underwent AVF creation for hemodialysis were prospectively recruited between March and November 2017. On preoperative duplex ultrasound, calcification in the arterial media within 5 cm of the planned anastomosis area was assessed. Clinical maturation was defined as the successful use of the fistula for $\geq$75% of the dialysis sessions during a month within 6 months after surgery. Radiological maturation was defined as a venous diameter of $\geq$0.4 cm and a flow volume of $\geq$500 mL/min. Flow volumes of the inflow artery and the cephalic vein were measured at 6 and 12 weeks after AVF creation.
Results: Eighteen patients with calcification and 29 patients without calcification were enrolled in this study. There was no significant difference in the clinical and radiological maturation between the groups. The flow volume of the inflow artery, measured at 6 weeks postoperatively, was significantly higher in the noncalcification group than in the calcification group ($P = 0.042$). The flow volume of the inflow artery in the noncalcification group was increased at 12 weeks postoperatively ($P = 0.091$). Flow volume of the vein was higher in the noncalcification group than in the calcification group, although it did not reach statistical significance.
Conclusions: In conclusions, preexisting arterial calcification did not adversely affect the AVF maturation. However, arterial calcification correlated with the flow volume of the inflow artery of AVF.

INTRODUCTION

An autogenous arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis due to the lower risks for infection and thrombotic occlusion. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend the placement of an AVF as the first choice for vascular access.[1] However, in the United States, a catheter is used for initial dialysis access in 80% of patients, and only a quarter of these patients result in a mature AVF afterward.[2] AVF maturation failure is the major barrier for the optimal use of a functioning AVF. Recent studies have reported maturation failure rates ranging from 20% to 60%.[3]

In previous studies, diameters of the cephalic vein and the inflow artery have shown to be correlating with AVF maturation.[4–7] In practice, the diameters of inflow artery and draining vein are evaluated

Declarations of interest: None.
Funding: This work was supported by Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center grant (26-2016-156).

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Ann Vasc Surg 2019; 58: 331–337
https://doi.org/10.1016/j.avsg.2018.10.057
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Manuscript received: October 9, 2018; manuscript accepted: October 31, 2018; published online: 13 February 2019

mainly during the preoperative vascular mapping. However, there is no generally accepted standard for what constitutes vascular mapping.[1] There are no definite criteria for a suitable artery for AVF, with limited studies investigating the influence of preexisting arterial pathology on vascular access for hemodialysis.[8] There are few studies with inconsistent results about the association of vascular calcification with AVF outcomes.[9–12]

The aim of this study is to investigate the effect of inflow arterial calcification on the maturation and flow volume changes of an autogenous AVF.

MATERIALS AND METHODS

Study population

This prospective observational study was conducted at a tertiary referral hospital in South Korea. The protocol of this study was approved by the Institutional Review Board of Boramae Medical Center (16-2017-30).

Patients between 30 and 80 years old with end-stage renal disease who underwent autogenous radiocephalic or brachiocephalic AVF creation were recruited between March and November 2017. Patients who underwent angioplasty at proximal arteries on the ipsilateral extremity before AVF creation were excluded from the study. Data of the demographic variables and comorbidities were collected.

Preoperative Duplex Ultrasound

All patients underwent preoperative duplex ultrasound (HD-15; Philips Medical system, Eindhoven, Netherland) performed by a single vascular surgeon. Based on the preoperative duplex ultrasound, we classified the patients into calcification and noncalcification groups. A thorough examination of the medial layer of the inflow artery within 5 cm from the planned anastomosis area was performed. When a pattern of calcification visualized as ''small white dots'' was present in more than 3 cm in length and one-fourth in circumference of the inflow arterial media, we classified the patients into the calcification group (Fig. 1). Patients with totally circumferential calcification in the inflow artery were excluded in this study.

The diameter and flow volume of the inflow artery were measured 5 cm proximally to the planned anastomosis site. The diameter of the cephalic vein was measured at every 5 cm segment from the wrist when radiocephalic AVF was planned or from the antecubital fossa when brachiocephalic AVF was planned. Patients with a radial artery diameter of >2.0 mm or a brachial artery diameter of >3.0 mm and a cephalic vein diameter of >2.0 mm on preoperative duplex ultrasound were eligible for enrollment.

Surgical Procedures

The site for the AVF is decided based on the diameter of the cephalic vein (i.e., >2 mm in diameter). An AVF was preferentially created in the forearm. However, the clinical assessment and patient's age were also considered while deciding the site. All AVFs were created by a single experienced vascular surgeon (I.M.J.) by performing a direct anastomosis between the end of the cephalic vein and the side of the radial or brachial artery.

Follow-ups and Study Outcomes

Duplex ultrasound was performed 6 and 12 weeks postoperatively. The diameter and flow volume of the inflow artery were measured 5 cm proximal to the anastomosis site. Diameter and flow volume of the cephalic vein were measured at the anastomosis site and at every 5 cm segment from the anastomosis site. Primary outcomes were successful clinical and radiological maturation. Clinical maturation was defined as fistula use with 2 needles for ≥75% of the dialysis sessions over a continuous 4-week period, with a mean blood pump speed of ≥300 mL/min, which was quoted from that of the Hemodialysis Fistula Maturation group.[3,10] The criteria can be satisfied at any time within 6 months after the surgery or 8 weeks after dialysis therapy initiation without any intervention procedures.[3,13] Radiological maturation was defined as a minimum venous diameter of ≥0.4 cm and a flow volume of ≥500 mL/min, which was known as University of Alabama at Birmingham criteria.[14,15] It was evaluated by a duplex ultrasound between 6 and 12 weeks after AVF creation. The secondary outcomes were changes in the flow volumes and minimal diameters of the inflow artery and the cephalic vein which were measured at 6 and 12 weeks after AVF creation.

Statistical Analysis

Continuous data were summarized as mean ± standard deviation or median with a range and compared using *t*-test or Mann–Whitney *U*-test. Categorical data were summarized as proportions and percentages and compared using the chi-squared test or Fisher's exact test. A P value <0.05 was considered statistically significant. All statistical

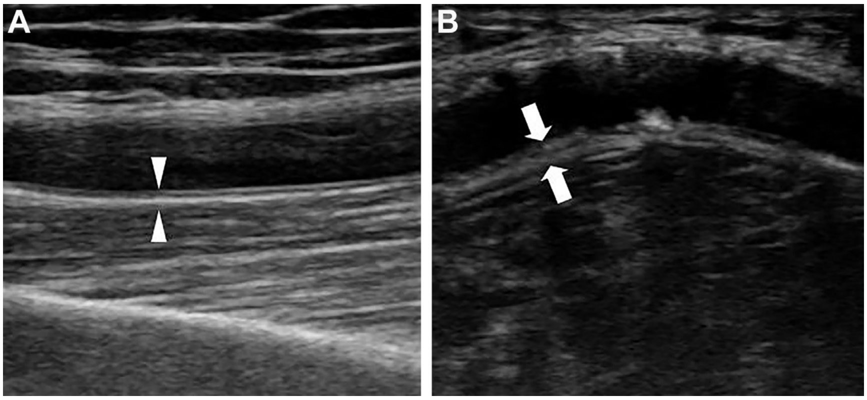

Fig. 1. Representative ultrasound imaging. **(A)** A longitudinal image shows intima and medial layers of brachial artery without calcification (*arrowheads*). **(B)** A longitudinal image shows calcifications in the medial layers of brachial artery (*arrows*).

analyses were performed using SPSS software, version 18 (IBM Corp, Armonk, NY).

RESULTS

Baseline Characteristics

A total of 86 patients underwent autogenous radiocephalic or brachiocephalic AVF creation during the study period. Among them, 50 patients were prospectively enrolled during the study period. In these patients, 1 patient underwent kidney transplantation 2 months after the AVF creation, 1 patient died of acute myocardial infarction 2 months after the surgery, and 1 patient was lost to follow-up. These patients were excluded from the analysis. Of the 47 patients, 18 patients were classified into the calcification group and 29 patients were classified into the noncalcification group. The baseline characteristics were similar between the groups except for the incidence of comorbidities. Patients in the calcification group were more likely to have coronary artery disease compared to those in the noncalcification group (Table I). The diameters of the inflow artery and cephalic vein and the flow volume of the inflow artery measured preoperatively on duplex ultrasound were similar between the groups (Table II).

Clinical and Radiological Maturation

Four patients in the calcification group and 1 patient in the noncalcification group had not started maintenance hemodialysis during the study period. Excluding them, clinical maturation was achieved in 13 of 14 patients (92.9%) and 27 of 28 patients (96.4%) in the calcification and noncalcification group, respectively. One patient in the calcification group discontinued the AVF use because of severe pain during hemodialysis, and 1 patient in the noncalcification group discontinued the AVF use because of prolonged hemostasis after dialysis. The time to first cannulation of AVF was 76.2 ± 32.2 days in the calcification group and 98.4 ± 37.9 days in the noncalcification group ($P = 0.051$). However, on analyzing including patients who were not on hemodialysis at the time of AVF creation, the time to first cannulation was 80.3 ± 36.1 and 81.2 ± 36.6 days, respectively ($P = 0.949$).

Radiological maturation was achieved in all patients in the calcification group and in 28 of 29 patients (96.6%) in the noncalcification group. Radiological maturation was evaluated at mean 67.5 ± 32.7 days after AVF creation. One radiocephalic AVF did not meet the criteria for radiological maturation with a cephalic vein diameter of 3.4 mm and flow volume of 547 mL/min measured 12 weeks after the surgery. There was no significant difference in the clinical and radiological maturation failure between the groups ($P = 0.999$) (Table III).

Surgical or radiological intervention was performed in 9 patients for significant stenosis or prominent accessory veins. The criteria for significant stenosis were >50% reduction in the luminal diameter and a peak systolic velocity ratio of >2.0.[16] The decision to ligate the accessory vein was made by a vascular surgeon based on the sonographic findings of an abrupt drop in the flow volume after the vein branching.[16] One patient in the calcification group and 9 patients in the noncalcification group underwent interventions to aid maturation ($P = 0.065$). All of them underwent balloon angioplasty for cephalic vein stenosis and 1 patient underwent branch ligation with balloon angioplasty. No patient

Table I. Baseline characteristics of 47 patients

	Calcification ($n = 18$)	Noncalcification ($n = 29$)	P value
Age, mean ± SD	62.2 ± 12.8	59.8 ± 11.4	0.503
Female, n (%)	3 (16.7%)	9 (31.0%)	0.324
Etiology of CKD, n (%)			0.070
Diabetes mellitus	13 (72.2%)	14 (48.3%)	
Hypertension	3 (16.7%)	1 (3.4%)	
Glomerulonephritis	0	2 (6.9%)	
Polycystic kidney disease	0	1 (3.4%)	
Others	1 (5.6%)	1 (3.4%)	
Unknown	1 (5.6%)	10 (34.5%)	
On HD at operation, n (%)	13 (72.2%)	13 (44.8%)	0.107
Comorbidities, n (%)			
Hypertension	17 (94.4%)	25 (86.2%)	0.636
Diabetes mellitus	13 (72.2%)	14 (50.0%)	0.220
Dyslipidemia	6 (33.3%)	8 (27.6%)	0.749
Peripheral arterial disease	2 (11.1%)	0	0.142
Coronary artery disease	9 (50.0%)	4 (13.8%)	0.017
Cerebrovascular accident	5 (27.8%)	4 (13.8%)	0.274
Smoking history, n (%)	4 (22.2%)	3 (10.3%)	0.404
Type of AVF, n (%)			0.999
R-C AVF	7 (38.9%)	11 (37.9%)	
B-C AVF	11 (61.1%)	18 (62.1%)	

HD, hemodialysis; CKD, chronic kidney disease; B-C AVF, brachiocephalic arteriovenous fistula; R-C AVF, radiocephalic arteriovenous fistula; SD, standard deviation.

Table II. Diameters and flow volume of inflow artery and cephalic vein measured preoperatively

	Calcification ($n = 18$)	Noncalcification ($n = 29$)	P value
Diameter, mean ± SD (mm)			
Inflow artery	3.57 ± 1.23	3.47 ± 1.10	0.751
Cephalic vein	3.33 ± 1.34	3.03 ± 0.75	0.801
Flow volume, mean ± SD (mL/min)			
Inflow artery	43.8 ± 33.1	44.8 ± 27.7	0.662

SD, standard deviation.

underwent surgical or radiological interventions for arterial lesions.

Diameters and Flow Volume

There were no significant differences in the minimal diameters of the inflow artery and cephalic veins measured at 6 and 12 weeks after AVF creation. The flow volume of the inflow artery measured at 6 weeks postoperatively was significantly higher in the noncalcification patients ($P = 0.042$). Additionally, there was a tendency toward increased flow volume of the inflow artery in the noncalcification group measured at 12 weeks postoperatively ($P = 0.091$). There was an increase in the flow volume of the cephalic vein in the noncalcification group measured at 6 and 12 weeks after AVF placement, although it did not reach a statistically significant difference (Table IV).

DISCUSSION

This study showed that arterial calcification was a significant influencing factor for increasing arterial flow volume after AVF creation. Few studies have investigated the effect of preexisting arterial calcification on AVF outcomes. Allon et al.[10] concluded that arterial calcification evaluated by pathology and ultrasound did not affect AVF outcomes. Choi et al.[11] showed that arterial calcification, evaluated by von Kossa staining, was a significant predictor of AVF failure. Georgiadis et al.[12] showed worsening of the clinical outcomes of radiocephalic AVF with calcification evaluated on plain 2-dimensional radiography. The results of these studies were inconsistent and the methods to evaluate the arterial calcification were varied. In clinical practice, the suitability of an artery for AVF is usually evaluated by duplex ultrasound. Plain radiography can detect calcification only when it is severe, and a pathologic examination is difficult to perform preoperatively. The strength of this study is the evaluation of arterial

Table III. Maturation of arteriovenous fistula

	Calcification ($n = 18$)	Noncalcification ($n = 29$)	*P* value
Not yet on HD, *n* (%)	4 (22.2%)	1 (3.4%)	
Clinical maturation, *n* (%)	$n = 14$	$n = 28$	0.113
Maturation	13 (92.9%)	27 (96.4%)	
Maturation failure	1 (7.1%)	1 (3.6%)	
Radiological maturation, *n* (%)	$n = 18$	$n = 29$	0.999
Maturation	18 (100%)	28 (96.6%)	
Maturation failure	0	1 (3.4%)	
Time to evaluation of radiological maturation, mean ± SD (days)	66.6 ± 39.5	68.1 ± 27.9	0.879
Time to first cannulation, mean ± SD (days)	76.2 ± 32.2	98.4 ± 37.9	0.051
Aiding intervention, *n* (%)			0.065
PTA	1 (5.6%)	9 (31.0%)	
Branch ligation	0	1 (3.2%)	

HD, hemodialysis; PTA, percutaneous transluminal angioplasty; SD, standard deviation.

Table IV. Hemodynamic outcomes of AVF

	Calcification ($n = 18$)	Noncalcification ($n = 29$)	*P* value
Diameter, mean ± SD (mm)			
Inflow artery			
6 weeks postoperatively	4.32 ± 0.99	4.76 ± 1.13	0.267
12 weeks postoperatively	4.55 ± 0.99	4.96 ± 1.12	0.242
Cephalic vein			
6 weeks postoperatively	5.97 ± 1.51	5.59 ± 1.43	0.405
12 weeks postoperatively	6.71 ± 1.60	6.18 ± 1.72	0.215
Flow volume, mean ± SD (mL/min)			
Inflow artery			
6 weeks postoperatively	609.2 ± 418.1	806.3 ± 383.8	0.042
12 weeks postoperatively	709.2 ± 440.1	908.9 ± 450.1	0.091
Cephalic vein			
6 weeks postoperatively	912.2 ± 288.9	1,039.8 ± 455.6	0.433
12 weeks postoperatively	1,175.11 ± 358.7	1,334.8 ± 715.3	0.945

SD, standard deviation.

calcification by duplex ultrasound and determining its effect on the AVF outcomes.

The prevalence of arterial calcifications in AVF is reported to be 14–23%.[17,18] Calcification is commonly found in the inflow arteries in AVF, but it has not been focused on when planning an AVF. Additionally, there is no standard scoring system for arterial calcification in the preoperative vascular mapping for AVF creation. Calcification in peripheral arterial diseases is evaluated based on the extent of calcium deposition and circumference of the involved vessels.[19,20] Arterial calcification is not rare and affects AVF outcomes; thus, it should be evaluated during vascular mapping for AVF and a validated quantitative scoring system should be developed.

Patients in the calcification group showed significantly decreased flow volumes of the inflow artery, compared to those in the noncalcification group. Vascular calcification is known to contribute to increased arterial stiffness, which leads to excessive shear stress, turbulence, and neointimal hyperplasia, and results in failure of arterial remodeling after AVF creation.[8,21–23] During the follow-up after AVF creation, the major focus is on the flow volume of the draining vein. However, a considerable increase in the blood flow and diameter of the inflow artery is also important for the successful maturation of AVF. Moreover, in the absence of sufficient increase in the arterial flow proximal to the AVF, a retrograde flow in the artery distal to the AVF can occur, leading to a steal phenomenon.[24] Previous studies have investigated the effect of arterial conditions, such as medial fibrosis and intimal hyperplasia, on AVF outcomes.[8,10,11,13,25,26] AVF failure is multifactorial and is not determined by any one of these pathologies.[9] Hence, a more comprehensive evaluation of the arterial pathology, apart from the diameter, is necessary when an AVF is planned.

In this study, there was no significant difference in the incidences of clinical and radiological maturation failure between the groups. Patients with severe circumferential calcification which was inappropriate for inflow artery were excluded. We presume that the calcification of the inflow artery was not heavy to show a significant difference in the initial usability in this study. It is necessary to determine whether arterial calcification influences the patency and increase in flow volume of the veins in a follow-up study over a longer term.

The time to first cannulation was shorter in patients with calcification. However, the difference was not significant when analyzed with the patients who were not on hemodialysis at the time of AVF creation. Urgent needs for vascular access in patients who were already on hemodialysis could have affected this result. Preexisting arterial calcification did not increase the number of aiding procedures for maturation. More surgical or radiological interventions were performed in patients in the noncalcification group, although it did not reach statistical significance. All the procedures were performed for venous stenosis and no procedure was performed for arterial lesions. Thus, it is difficult to determine whether arterial calcification is associated with frequent interventions for maturation.

There are risks of arterial crack and insecure anastomosis in AVF creation with calcified artery. Gołębiowski et al.[27] reported the result of sleeve method, which was performed by advancing the end part of the artery into the vein end, in advanced atherosclerotic artery. In this study, we excluded patients with severe circumferential calcification, thus a usual end-to-side anastomosis method was used in all patients. We just strictly followed the principle of vascular anastomosis. We minimized the manipulation of artery and sutured from inside to outside in arteries. In addition, vessel loops were used for proximal and distal arterial control instead of vascular clamps to reduce the risks of arterial cracks and vasospasm.

Akin et al.[28] reported the effect of transdermal glyceryl trinitrate in AVF outcomes. Nitrate derivatives are known to act by indirectly releasing nitric oxide and by antagonizing the rise in smooth muscle cell calcium.[29] Other agents such as papaverine or lidocaine were used to prevent arterial vasospasm. In this study, we use topical application of lidocaine to prevent or reverse vasospasm after anastomosis in some patients. One hypothesis is that atherosclerosis makes arteries too stiff to spasm.[30] It is worth comparing the severity of vasospasm and the effect of vasodilators between calcified and normal arteries in AVF creation.

Our study had several limitations. First, it is a prospective study but with a small number of patients with a relatively short follow-up duration. Second, as mentioned earlier, there was no clear definition or scoring system for preexisting arterial calcification in AVF. Without definite criteria, it is difficult to be totally objective in ultrasound examination. Third, we excluded 6 patients with severe circumferential calcification, thus the effect of calcified artery on the AVF outcomes was lessened in our analysis. Finally, more patients in the calcification group had a history of coronary artery disease, which could affect the cardiac function and flow volume of AVF.

In conclusion, preexisting arterial calcification did not adversely affect the AVF maturation. However, the inflow arterial calcification evaluated on preoperative duplex ultrasound inversely correlated with the increase in flow volume of the inflow artery in AVF. With the results of this study, we recommend a close observation for increase in arterial flow volume when a calcified artery is seen on preoperative duplex ultrasound.

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