

## Challenges and possibilities in Vascular Access Creation for Patients on Chronic Dialysis

Kybartienė-Mačiulaitė Sa<sup>1</sup>, Stankuvienė A<sup>1</sup>, Kuzminskis, V<sup>1</sup>, Bumblytė, IA<sup>1</sup>,  
Venclauskienė, A<sup>1</sup>, Buitkus, M<sup>2</sup>, Kaupas, R<sup>2</sup>, Žurauskas, E<sup>3</sup>,

<sup>1</sup>Department of Nephrology, Hospital of Lithuanian University of Health Sciences Kauno klinikos, Kaunas, Lithuania

<sup>2</sup>Department of Radiology, Hospital of Lithuanian University of Health Sciences Kauno klinikos, Kaunas, Lithuania

<sup>3</sup>Department of Pathology, Forensic Medicine and Pharmacology, Vilnius University Faculty of Medicine, Vilnius, Lithuania

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**Abstract.** Background and objectives: The population of patients on chronic hemodialysis (HD) is still growing. It is well known that the best vascular access for these patients is native arteriovenous fistula (AVF). Until now, there have been many discussions why some AVFs never become suitable for adequate HD. The aim of this study was to find the factors that could influence primary AVF dysfunction in patients on chronic hemodialysis.

**Materials and Methods:** Patients with chronic kidney disease stage V, older than 18 years and scheduled for the first AVF were invited to participate in the prospective observational study ( $n = 50$ ). At the time of AVF creation, a surgeon obtained specimens of the vein, which were fixed in 10% formalin and processed for light microscopy. A pathologist examined the vein for intimal hyperplasia and vein medial fibrosis using Von Gieson staining. Ca, P and PTH were investigated in the patients' blood. Before AVF formation, vascular mapping by ultrasound was performed. AVF suitability for dialysis within 3 months of AVF creation was determined clinically according to general recommendations

**Results:** Of 50 study patients, 38 AVFs successfully matured (76%), and in 12 cases (24%) early fistula dysfunction was diagnosed. According to the study data, early AVF dysfunction was not associated with arterial and vein diameters before fistula creation ( $P > 0.05$ ) and vein intimal hyperplasia or media fibrosis ( $P > 0.05$ ). The patients' gender ( $P = 0.273$ ), age ( $P = 0.228$ ) and the main kidney disease ( $P = 0.321$ ) were not statistically significant for early AVF dysfunction frequency.

**Conclusions:** 24% of the patients developed early AVF dysfunction. Neither arterial and vein diameters, nor vein intimal hyperplasia and media fibrosis were associated with early AVF dysfunction. Further investigations of the role of these factors in a large number of patients are necessary. Although this study did not demonstrate any benefit, preoperative vascular mapping is still recommended in order to prevent early AVF dysfunction for the patients with end-stage renal failure because we only used sufficient diameters vascular for creation arteriovenous fistulas.

### Introduction

More than 940 patients per million population in Europe are affected by end-stage renal disease and live on chronic renal replacement therapy. Approximately 80% of these patients are treated chronically by hemodialysis [1]. The total number of patients on HD in Europe exceeds 500,000 and it increases annually at a constant rate of 7% [2].

Native AVFs are recognized as the optimal vascular access for HD because they are associated with lower morbidity and mortality than catheters and grafts [2, 3]. Multiple factors determine the vascular access type: access to a nephrologist when diagnosed kidney disease, patient anatomy and education, local surgical expertise. DOPPS I data indicated that in Europe HD patients were threefold more likely to have an autogenous AVF as compared with North America. However, between DOPPS I and III, the

use of AVF increased to 47% in the United States and decreased slightly from 80% to 74% in Europe [4]. Nonetheless, even if we create AVF in time, the durability of AVFs is far from optimal with 1-year primary patency rates ranging from 60 to 65% [5, 6]. In fact, the numbers are too optimistic, as they often do not account for fistulas the maturation failure of which contributes significantly to the dismal patency rates of AVFs, as illustrated by a recent multicenter study, which revealed that 60% of AVFs were not suitable for dialysis between 4 and 5 months after surgery. Early failure of fistulas due to thrombosis or inadequate maturation is a barrier to increasing the prevalence of fistulas among patients treated with HD [7].

Surgeons in our hospital create more than 200 native AVFs every year. The rate of primary dysfunction varies from 10 to 24% [8]. The aim of this

study was to find the factors that could influence primary AVF dysfunction, including demographic factors, laboratory blood tests and morphological changes in the vein wall before operation.

## Materials and Methods

### Study Population

The study was performed at the Hospital of the Lithuanian University of Health Sciences in collaboration with the National Center of Pathology, Affiliate of Vilnius University Hospital Santaros Klinikos.

The study assessed 50 predialysis patients at the Hospital of the Lithuanian University of Health Sciences, Department of Nephrology, where they were diagnosed with end-stage chronic kidney disease and scheduled for HD procedures. The patients were older than 18 years and underwent their first AVF formation. They had not undergone any renal replacement therapies before.

Demographic data including age, kidney disease and comorbid conditions associated with vascular fibrosis were collected from medical records.

### Preoperative Vascular Mapping

All the patients underwent sonographic preoperative vascular mapping according to the standard UAB protocol. Vascular measurements were performed with the patient in a seated position, and the arm resting comfortably on an adjustable instrument stand. Arterial diameters were measured at the radial artery in the wrist. A tourniquet was moved sequentially up the arm to measure venous diameters at several locations in the forearm and the upper arm, and to evaluate for venous stenosis or thrombosis. All the measurements were recorded on a worksheet, which was provided to the surgeon prior to a patient's preoperative visit. Creation of an AVF required a minimum arterial diameter of 2 mm and a minimum venous diameter of 2.2 mm. Patients with evident stenosis or thrombosis in the vein and with calcification in the site of AVF formation of the artery were excluded.

### Specimen Collection

At the time of surgery, a venous specimen of 3–5 mm was obtained and fixed in formalin. AVF surgery was performed by making a direct anastomosis between the end of the *v. cephalica* and the side of the *a. radialis*.

### AVF Evaluation

Postoperative duplex ultrasound was performed 1–3 days after the surgery with measurement of the diameter and the vein lumen. We checked the blood flow rate in a brachial artery (in the upper third of the arm). Both preoperative and postoperative duplex ultrasounds were performed by 2 experienced radiologists.

Maturation of AVFs was evaluated by clinical criteria 12 weeks after the surgery. Early dysfunction of the fistula was considered as the cases when the lumen of the vein was too small, and it was not possible to puncture the vein and/or the blood flow during HD was less than 350 mL/min, and an adequate HD procedure was unavailable. The suitability of an AVF for HD was rated by dialysis nurses and nephrologists.

### The Sampling of the Laboratory Tests

Laboratory blood tests that could have influence on the vessel wall quality were performed at the time of admission to the hospital for the creation of an AVF. Tests included calcium, phosphorus, parathyroid hormone, markers of inflammation (CRP and leukocytosis) and the hemoglobin level.

### Histomorphometric Analysis of Vein Specimens

Cross-sections of venous samples were fixed in 10% neutral buffered formalin and processed for light microscopy. A pathologist who was unaware of the clinical information and AVF outcomes performed all the histologic evaluations. All tissue samples were stained with H&E.

Whole-slide specimens were scanned at a 20x magnification using a digital scanner (ScanScope® XT, Aperio Technologies, Vista, CA, USA) and the obtained digital images were archived on the server (Spectrum 11.1.0.751, Aperio). Digital analysis was performed by using *Aperio Colocalization* and *Aperio Positive Pixel Count V9* algorithms.

For evaluation of the connective tissue in the vascular smooth muscle, digital slides were annotated by the marking vascular smooth muscle (intimae and surrounding connective tissue were not analyzed). The *Aperio Colocalization* algorithm was calibrated to classify each pixel into 3 categories. The algorithm reports the area of every category separately and areas of every possible combinations of categories. The total percentage of the connective tissue in the vascular smooth muscle was calculated as a sum of the first and the third categories, which is the best way to detect the connective tissue in the vascular smooth muscle. The results are given as percentage.

### Statistics

Statistical analyses were performed using IBM SPSS software version 22. A statistically significant relation between early AVF dysfunction, patients' age groups and the main kidney disease was calculated using the precise chi test. Patient's age, laboratory blood tests, vascular diameters, vein intimae thickness, medial fibrosis and hyperplasia are presented in median. The Mann-Whitney test was used to compare age, diameter of the vein, intimae hyperplasia rate and fibrosis scores. A *P* value < 0.05 was considered statistically significant.

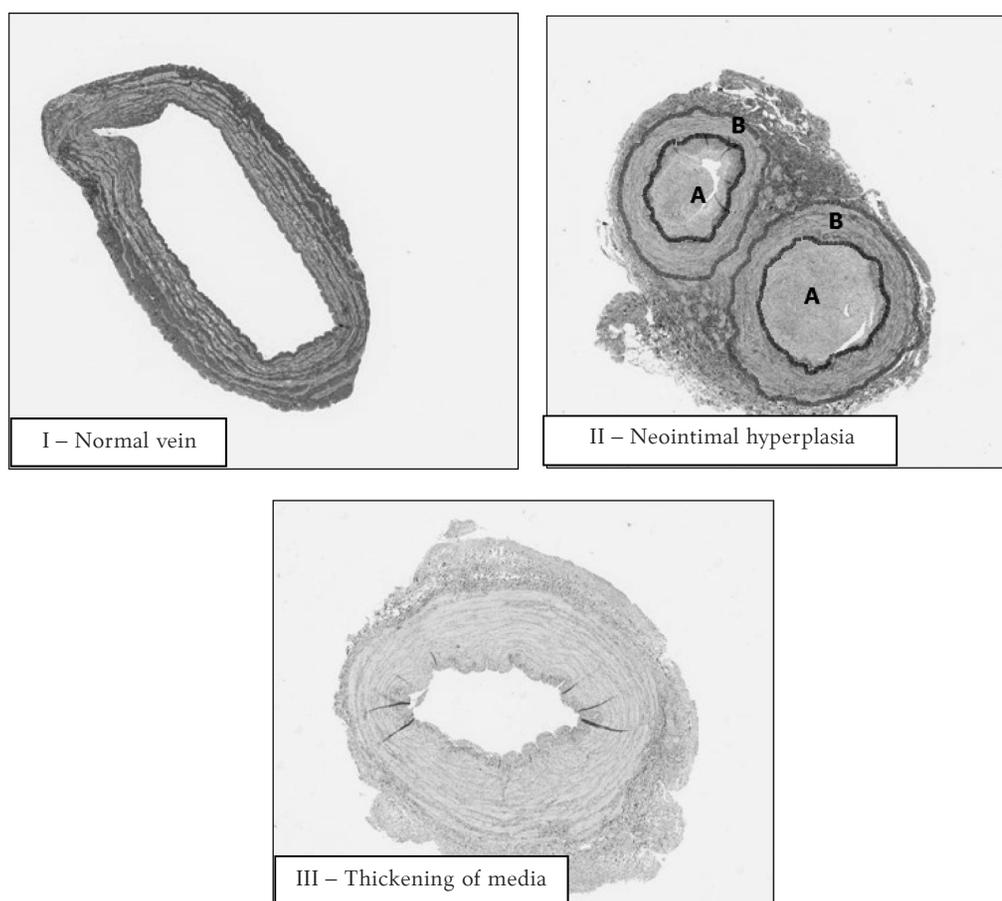


Fig. 1. **I** – histopathology of vein specimens from a patient with no CKD; **II** – very severe neointimal hyperplasia in a patient with ESRD at the time of AV access placement (A – lumen of the vessel plus the neointimal area; B – the intima-media area of the vessel); **III** – aggressive thickening of media and significant luminal stenosis in a patient with ESRD at the time of AV access placement.

### Results

Of 50 study patients, 38 AVFs (76%) successfully matured and were suitable for HD procedures, and in 12 cases (24%) AVFs did not mature in a 3-month period. Early dysfunction of AVF was diagnosed.

The comparison of groups where AVF was successfully matured and the group of early dysfunction of AVF demographics characteristics are shown in Table 1. The median age was 67 years in the group of successful AVF maturation and 65.5 in the group of nonmaturing AVF. The majority of

Table 1. Comparison of patients in groups according to AVF maturation

	Mature AVFs, n = 38 (%)	Nonmaturing AVFs, n = 12 (%)	P
Gender			
Men	26 (67.6)	6 (50)	0.273
Women	12 (32.4)	6 (50)	
Age (y)	67 (28–88; 65.49)	65.5 (38–79; 64.17)	0.771
< 65	14 (35.1)	2 (16.7)	0.228
≥ 65	24 (64.9)	10 (83.3)	
The main kidney disease			
Parenchymal kidney disease	16 (43.2)	7 (58.3)	0.321
Vascular kidney disease	16 (43.2)	2 (16.7)	
Diabetes	5 (13.5)	3 (25)	

the patients had chronic parenchymal kidney disease ( $n = 23$ ): 43.2% in the successfully maturing group and 58.3% in the group of nonmaturing AVF ( $P > 0.05$ ). Diabetes, which was regarded as a risk factor for early AVF dysfunction, accounted for 16% of all patients and the number was similar in both groups ( $P > 0.05$ ). Patient's age, gender and main kidney disease did not have a statistically significant association with early AVF dysfunction.

The results of laboratory blood tests are shown in Table 2. The level of calcium (median 2.0 mmol/L vs. 2.08 mmol/L;  $P = 0.56$ ) or phosphorus (median 1.58 mmol/L vs. 1.73 mmol/L;  $P = 0.82$ ) were not statistically significantly different between the groups of mature and nonmature AVFs. The level of anemia (Hb median 94 g/L vs. 96.5 g/L;  $P = 0.67$ ) or the count of platelets (median  $200 \times 10^9$  vs.  $197 \times 10^9$ ;  $P = 0.46$ ) had no statistically significant impact on early AVF dysfunction development.

Preoperative duplex ultrasound was performed in all 50 patients before AVF creation. This examination was performed to evaluate the diameters of the vessels and their patency. There was no difference between both groups in vein and artery diameters (vein diameter median 2.63 mm vs. 3.21,  $P = 0.2$ , and artery 2.55 mm vs. 3.0 mm,  $P = 0.31$ ). Morphological and structural changes that could have predetermined early dysfunction or successful maturation of AVFs could have been thoroughly examined in this way. The results are shown in Table 3. We did not observe more intimal hyperplasia in the group of nonmaturing AVFs (median 45 microns in the group of maturing AVFs vs. 55.5 microns in

the group of nonmaturing AVFs,  $P = 0.8$ ) compared with the group of maturing AVFs. Medial fibrosis of varying degrees was observed in all the vein specimens obtained at the time of AVF creation. The mean medial fibrosis for the study population was 27.65% (range, 0.1 to 72.8%) and did not differ significantly between nonmaturing and mature AVFs ( $P = 0.2$ ).

## Discussion

**Primary dysfunction rate.** Primary failure of AVF was diagnosed in 24% of the patients in our study. Our center rate 10 years ago was definitely better than now. Then, primary failure of AVFs was diagnosed only in 14.6% of the patients [7]. However, these rates are not exceptional in comparison with other centers in Europe and the USA. The reported AVF maturation rate varies widely, from 30% to 90% [8]. As positive opinions on native AVFs for hemodialysis continue to increase, the rate of primary failures of AVFs also increases [10,11]. The comparison of different authors and in different periods is presented in Table 4.

While criteria by which a surgeon assesses the suitability for creating a native AVF are being liberalized and the patients on HD are changing (hemodialysis is more often started in older patients who have more comorbid conditions), the rate of nonmaturing AVFs is increasing [12, 39].

Earlier (1966), primary fistula failure was approximately only 11%. Later (1980–2000), primary failure rates were reported to range from 10 to 25% [9]. In more recent reports, the incidence has been

Table 2. Laboratory tests findings before AVF creation

	Mature AVFs, n = 38	Nonmaturing AVFs, n = 12	P
HGB (g/L)	94 (56–130; 94.46)	96.5 (56–157; 99.17)	0.675
PLT $\times 10^9$	200 (88–387; 222.57)	197 (145–669; 276.58)	0.464
WBC $\times 10^9$	6.96 (3.89–13.14; 7.35)	8.56 (5.74–33.3; 12.75)	0.081
Ca (mmol/L)	2.05 (1.5–2.5; 2.040)	2.08 (1.9–2.6; 2.105)	0.564
P (mmol/L)	1.58 (0.99–3.55; 1.756)	1.73 (1.03–2.29; 1.68)	0.825
PTH (pmol/L)	31.02 (4.18–142.33; 37.06)	27.9 (8.65–75.33; 32.33)	0.567
CRP (mg/L)	10.2 (1–170; 26.203)	26.365 (2.26–133.15; 38.53)	0.209

Table 3. Preoperative feature of the vasculature

	Mature AVFs, n = 38	Nonmaturing AVFs, n = 12	P
Forearm arterial diameters (mm)	2.55 (1.7–5.1; 2.731)	3 (2.1–4.1; 2.892)	0.31
Forearm vein diameters (mm)	2.63 (1.85–3.2; 2.812)	3.21 (2.2–4.8; 2.675)	0.2
Vein intimal thickness (um)	45 (16–193; 54.879)	55.5 (12.5–440.5; 94.545)	0.8
Vein medial fibrosis (%)	24.11 (0.1–72.8; 22.714)	31.2 (5–56.7; 30.134)	0.2
Vein media hyperplasia (um)	322.25 (154.5–507; 326.67)	255.5 (170–415; 278.727)	0.08

Table 4. The range of primary dysfunction of AVFs in different periods (7.9) according to the data of different authors

Study and authors	Number of patients	Time of the study	The range of primary dysfunction (%)
Schild et al.	154	1996–2001	31
Biuckians et al.	377	2005	52
DAC	877	2003–2007	60
Kybartiene et al.	272	2000–2010	15
Kybartiene et al.	50	2015	24

higher, ranging from 20 to 60% [13]. Thus, the question arises as to what is the main problem of such a dramatically increasing rate in primary dysfunction. Many authors know the answer: earlier the average age of a dialysis patient was 43 years, and almost all of them had chronic glomerulonephritis as the main kidney disease. Now dialysis patients are much older (> 70 years), 75% of patients on chronic HD have 5 or more comorbidities, 90% have cardiovascular disease, and 50% have diabetes [9,13,14,15].

**Vascular mapping.** Due to this difficult situation, vascular mapping prior to AVF creation is strongly recommended by many authors. We did not find any relation between vascular diameters and early AVF dysfunction. The reason we found the diameter of vessels not statistically significant could probably be explained by the use of vessels of a sufficient diameter only. The optimum diameter of an artery was 2 mm and more, and the diameter of a vein was 2.5 mm and more. The vessels of these diameters are considered suitable even for obese or diabetic patients [16,17]. If diameters of the vessels were unsuitable or thrombosis of the vein was present, the localization of AVF formation was changed. Qualification of patients for fistula creation must be based on physical and imaging examination by Doppler ultrasound results [18]. Many other authors recommend veins of minimum 2.5 mm and arteries of minimum 2 mm in diameter [19,20]. However, there is no agreement concerning the threshold, i.e., the minimal diameters of the vessels used for forearm anastomosis. Therefore, in some studies, patients with vessels of as small as 1.5 mm in diameter are also qualified for AVF creation [21]. It would be advisable to measure the blood flow rate and peak systolic velocity that would help in predicting successful maturation and the survival rate of an AVF [16].

**Older patients.** HD has special implications for older patients, who constitute the fastest growing sector of the incident end-stage renal disease population [22]. In our study, we did not find significant differences in patients' age and AVF maturing. The increased life expectancy of patients with chronic illnesses has resulted in a considerable increase in the number of older patients requiring dialysis. Improvements in dialysis care have also contributed

to the numbers of older dialysis patients. They are more likely than younger individuals to have poor quality arm veins because of prior medical interventions and to have atheroma or medial calcification affecting their arteries [23]. Older patients exhibit problems that may compromise the success of dialysis access surgery, such as arteriosclerosis, poor quality veins, thin skin, and comorbidities [24]. For these reasons, many older patients have HD access through a permanent catheter. However, one study has shown that patients older than 75 years with native vascular access can have patency similar to that of younger patients [25]. In the study, patients older than 80 years were found to have vasculature that was suitable for autogenous access creation. There were no significant differences in patency between forearm and upper arm access or between patients with and without diabetes mellitus [26].

**Patients with diabetes mellitus (DM).** In our study, we had only a few cases of diabetes mellitus and we did not find any influence on AVF maturing and early fistula dysfunction. The large systemic literature review was done about diabetic patients on chronic HD and possibilities to create well-functioning autogenous vascular access. A total of 13 studies comprising over 2,800 participants with DM were reviewed in detail and included in the review. Diabetic patients using a dialysis catheter were found to apparently experience a higher risk of death and infection compared with patients who successfully achieved and maintained an arteriovenous fistula as dialysis access [27]. Ravani et al. [28], Dieh et al. [29] and Konner [30] have reported lower patency rates of AVF among DM versus non-DM. On the other hand, Murphy and Nicholson [31], and Field et al. [32] have reported similar AVF patency rates between DM and non-DM patients.

**Pre-existing and postoperative intimal hyperplasia (IH).** Preoperative endothelial proliferation in the vein did not have any clinical significance in our study. Interestingly, pre-existing IH is frequently found in veins prior to vascular access creation, but its contribution to the pathogenesis of access failure is still controversial [21, 33, 34, 41]. It is believed that stenosis results from intimal hyperplasia and/or insufficient outward remodeling [35]. However, the underlying mechanism controlling the development

and hyperplastic expansion of the intima after vascular access creation are not well understood. The histologic hallmark of this vascular pathology is the aggressive accumulation of myofibroblast-like cells in the inner layers of the vessel [36, 37]. A study performed in Germany analyzing complications of AVFs in the first 3 months after surgery concluded that aggressive endothelial hyperplasia was the main reason for early complications of AVF [37]. Nonetheless, Tabbara et al. proved that at the time of surgery neointimal hyperplasia was found in 98% of cases [38] and did not have any influence on early AVF dysfunction and further performance of the AVF. Allon et al. researched a large group of patients and proved that intimal hyperplasia at the time of surgery did not have any influence on the development of early stenosis of AVF [39]. The literature review analyzing studies of biological processes in the first days/weeks after the formation of AVF acknowledged that capability for vascular remodeling is more relevant than neointimal hyperplasia [40]. In another study, the association between pre-existing IH and AVF outcomes was studied in 57 patients [21]. Intimal thickness in these tissues ranged from

0 to 0.66 mm, with concentric IH observed in 98% of the patients. There were no differences between patients with IH and without IH in terms of demographics, comorbid conditions, vascular access characteristics or concurrent medications. Pre-existing IH measured as maximal intimal thickness or the intima-media ratio was not associated with age, sex, or DM [33].

### Conclusions

Despite the fact that we investigated a number of factors that could affect AVF maturation, we did not answer the question which of them are the most important. Patients' age, gender, and the main kidney disease were not statistically important for early AVF dysfunction. We checked the status of the vein wall before AVF creation operation, but intimal and media hyperplasia or media fibrosis were not statistically significant factors for AVF maturation.

Further studies are needed to find the factors or combinations thereof, which may be significant for the development of early AVF dysfunction.

The study was done with the permission of Biomedical Research Ethics Committee.

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