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Treatment of failing arterio-venous dialysis graft by angioplasty, stent, and stent graft: Two-years analysis of patency rates and cost-effectiveness

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Abstract. The objective of this prospective randomized single-center study was to compare primary and secondary patency rates, number of percutaneous transluminal angioplasty (PTA) interventions and cost-effectiveness among PTA, deployment of a stent, or a stent graft in the treatment of failing arteriovenous dialysis grafts (AVG) due to restenosis in the venous anastomosis or the outflow vein. Altogether 60 patients with failing AVG and restenosis in the venous anastomosis or the outflow vein were randomly assigned to either PTA, placement of a stent (E-Luminexx®) or stent graft (Fluency Plus®). After the procedure, patients with stent or stent graft received dual antiplatelet therapy for the next three months. Follow-up angiography was scheduled at 3, 6, and 12 months unless requested earlier due to suspected stenosis or malfunction of the access. Subsequently, angiography was performed only if requested by the clinician. During a median follow-up of 22.4 (IQR=5.7) months patients with PTA, stent, or stent graft required 3.1±1.7, 2.5±1.7, or 1.7±2.1 (P=0.031) secondary PTA interventions. The primary patency rates were 0, 18 and 65% at 12 months and 0, 18 and 37% at 24 months in the PTA, stent, and stent graft group respectively (P<0.0001). The cost of the procedures in the first two years was €7,900±€3,300 in the PTA group, €8,500±€4,500 in the stent group, and €7,500±€6,200 in the stent graft group (P=0.45). We conclude that the treatment of failing dialysis vascular access by the deployment of a stent graft significantly improves its primary patency rates and decreases the number of secondary PTA interventions; however, the reduction in costs for maintaining AVG patency is not significant.

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Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CI, confidence interval; DA, dialysis access; HR, hazard ratio; IQR, interquartile range; PTA, percutaneous transluminal angioplasty

Key words: vascular access, hemodialysis, angioplasty, stent, stent graft, stenosis, cost-effectiveness

Introduction

Hemodialysis is the most common treatment of patients with end-stage renal disease. In most of them the circulation is accessed through an arteriovenous fistula (AVF) or a graft (AVG) created on the upper limb (1,2). Although there is no better entry point for dialysis than a functional dialysis access (DA) on upper limb, its performance is far from perfect with nearly all patients requiring at least one percutaneous intervention with a subsequent primary patency rate of 23% at 12 months (3-5).

Despite great effort that had been devoted to improving the durability of DA, for long percutaneous transluminal angioplasty (PTA) had been the mainstay of DA stenosis treatment. The proposed deployment of a stent in the stenosis was initially met with little success. Further studies showed that only nitinol stents might deliver improved patency rates (6,7). Further development based on the promising bare nitinol stent was crowned by the design of a covered stent graft. Initial promising results were confirmed in a randomized multicenter trial that showed significant improvement of overall patency rates and freedom from subsequent interventions in short-term (8). The benefit of a stent graft deployment in a stenosed DA had been replicated in further studies and scenarios (9). However, the efficacy of the use of stents or stent grafts in the treatment of DA had been questioned due to the high cost of the devices and a limited number of randomized studies with long-term endpoints (10).

The objectives of this independent study were to compare three options for the treatment of failing AVG due to restenosis in the venous anastomosis or the adjacent segment of the outflow vein by PTA, deployment of a stent, or a stent graft with regard to primary and secondary patency rates, the number of therapeutic interventions (either PTA ± thrombolysis) required to maintain vascular access patency, and the cost of maintaining the vascular access.

Materials and methods

This prospective single-center study was approved by the Ethics Committee of the General University Hospital in Prague (60/12 IGA MZ ČR VFN), it was conducted in accordance with the Declaration of Helsinki, and all patients signed informed consent. Between 2013 and 2015 a total of 60 subjects were randomized in three study groups according to the strategy for treatment of the restenosis in the venous anastomosis or outflow vein of prosthetic AVG. The inclusion criteria were: i) Age above 18 years; ii) AVG located in the upper extremity; iii) restenosis in the venous anastomosis or adjacent segment of the outflow vein up to the axilla; iv) at least 2 previous PTAs during the previous year; v) last PTA of the stenosis <3 months and vi) referral for angiography due to malfunction of the fistula (low flow rate, elevated venous pressure during dialysis, increased intradialytic recirculation). The exclusion criteria were: i) life expectancy <1 year; ii) thrombosed fistula; iii) previous infection of AVG; iv) history of adverse reaction to iodinated contrast material and v) blood coagulation disorder.

The patients were randomly assigned to either continued PTA treatment, placement of a stent or stent graft.

Angiography and intervention. The procedures were performed by three experienced interventional radiologists with 11 to 32 years' experience at a tertiary academic center. In the supine position, after local disinfection, one cannula was placed in the arterial (inflow) segment of the graft in an antegrade direction. Angiography was performed on a standard angiography system (Axiom Artis MP, Siemens AG, Munich, Germany) during injection of 10-15 ml of Iomeron 400 (Iomeprol, Bracco Imaging, Konstanz, Germany) in anterior-posterior and oblique projections centered on the graft and the outflow vein as a digital subtraction angiography with a frame rate of 1/s.

PTA was performed from the same access using a balloon catheter (Optimed, Ettlingen, Germany; Boston Scientific, Marlborough, MA, USA) of appropriate diameter (7.3±0.7 mm; Fig. 1). In the stent group, a self-expanding nitinol stent (E-Luminexx® Vascular Stent, Bard Peripheral Vascular, Tempe, AZ, USA) with a diameter of 8.3±0.9 and length of 55±19 mm (Fig. 2) was implanted. In the stent graft group, a stent graft with similar design additionally covered by carbon-impregnated ePTFE (Fluency® Plus Endovascular Stent Graft, Bard Peripheral Vascular, Tempe, AZ, USA) with a diameter of 7.7±0.6 and length of 79±29 mm was used. If necessary, post-dilatation was performed by a non-compliant balloon catheter. The angiograms were evaluated by one radiologist who measured the diameter of the stenosis before and after PTA and the reference diameter of the adjacent segment.

Follow-up. After implantation of a stent or stent graft, a dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg daily) was administered for the next three months in all patients. If anticoagulation therapy was required for other reasons, it was continued. PTA patients either continued their antiplatelet or anticoagulant therapy or received at least one antiplatelet agent.

Follow-up angiography was scheduled 3, 6, and 12 months after the initial procedure unless requested by the referring physician earlier due to suspected restenosis (ultrasound) or malfunction of the fistula (low flow rate <600 ml/min, elevated dynamic venous pressure during dialysis, increased intradialytic recirculation, prolonged puncture site bleeding after hemodialysis) (11). Later, angiography was performed only if requested by the clinician. During the follow-up procedures, we performed angiography and decided on further treatment (no intervention, PTA, thrombolysis) based on angiographic findings. In one patient, a suspected infection of the stent graft was successfully treated with antibiotic therapy. One patient from the stent group withdrew from the study.

The endpoints were defined as follows: i) primary and secondary patency rates; ii) the number of therapeutic interventions (either PTA ± thrombolysis) required to maintain vascular access patency and iii) the cost of maintaining the vascular access calculated as the cost of the primary procedure (€1,210 for PTA, €2,667 for stent, and €3,475 for stent graft) and subsequent PTAs (€1,210). Primary patency was defined as the time from the index procedure to the first access failure or percutaneous intervention required to maintain its patency. Secondary patency was defined as the time from the index procedure to the abandonment of the AVG.

Statistical analysis. Statistical analysis was performed in SPSS 19 (IBM Corp., Armonk, NY), MedCalc 15 (MedCalc Software, Ostend, Belgium), and GraphPad Prism (GraphPad Software, La Jolla, CA, USA). Normality of the data was tested using D'Agostino's K2 test. To test for statistical significance among the study groups, we used ANOVA (with Bonferroni post hoc tests) or the Kruskal-Wallis test (with Dunns post hoc tests). Dichotomous variables were tested using the Fisher-Freeman-Halton test. Life table analysis was performed using the log-rank test and presented in a Kaplan-Meier estimator. Multivariable analysis was performed by Cox proportional hazard regression model using the forward likelihood ratio method on baseline characteristics and data from the primary interventions. P<0.05 was considered to indicate a statistically significant difference.

Results

The patients were 64±12 years old and 41 (71%) were women. There was no significant difference between the groups in the baseline data (Table I). In all patients, the primary intervention was technically successful (Table II). During a median follow-up of 22.4 [interquartile range (IQR)=5.7] months patients with PTA, stent, or stent graft required 3.1±1.7, 2.5±1.7, or 1.7±2.1 (P=0.031) secondary PTA interventions, respectively. The primary patency rates were 0, 18, and 65% at 12 months and 0, 18, and 37% at 24 months in the PTA, stent, and stent graft group respectively (P<0.0001; Fig. 3). The secondary patency rates were 94, 84, and 89% at 12 months and 94, 84, and 79% at 24 months (P=0.58; Fig. 4). The cost of the procedures in the first two years was €7,900±€3,300 in PTA group, €8,500±€4,500 in stent group, and €7,500±€6,200 in stent graft group (P=0.45).

Survival analysis showed that patients with stent graft had better primary patency rates (P<0.0001; Fig. 3), but there was

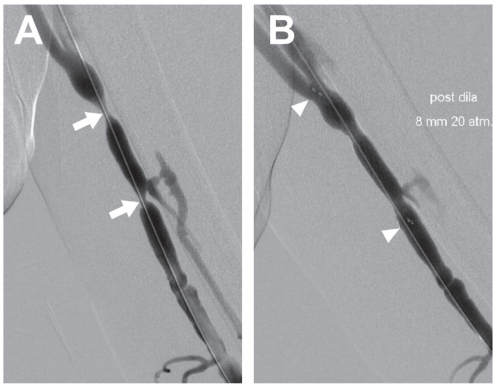

Figure 1. Angiography of AV graft (A) prior to and (B) following deployment of a nitinol stent (diameter, 8 mm; length, 60 mm, arrowheads) with a resolution of two stenoses in the outflow vein (arrows). AV, arteriovenous dialysis grafts.

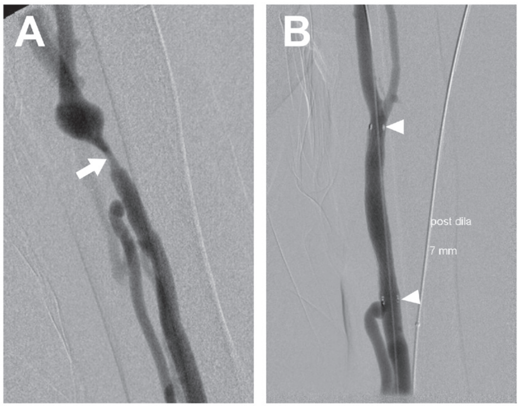

Figure 2. Angiography of AV graft (A) prior to and (B) following deployment of a stent graft (diameter, 7 mm; length, 80 mm, arrowheads) with resolution of a stenosis and aneurysm in the outflow vein (arrow). AV, arteriovenous dialysis grafts.

no difference in the secondary patency rates among the groups (P=0.58; Fig. 4). Multivariable Cox regression analysis identified the following predictors of primary patency: residual stenosis after initial PTA [hazard ratio (HR)=1.048; 95% CI 1.013 to 1.084; P=0.007], diameter of the reference segment adjacent to the stenosis (HR=0.498; 95% CI 0.306 to 0.813; P=0.005), and outflow to the superficial venous system vs. deep venous system (HR=0.457; 95% CI 0.233 to 0.894; P=0.022) with model significance of P=0.005 (Table III).

Discussion

In this study, we compared the mid-term performance of PTA, bare stent, and stent graft in the treatment of restenosis in the venous anastomosis or the adjacent segment of the outflow vein of upper limb AVGs. We showed that patients with stent graft required less subsequent PTA interventions but the reduction in cost was not statistically significant. We further identified predictors of primary patency rate.

Hemodialysis is the most common treatment of patients with end-stage renal disease. Maintaining dialysis access is necessary for all patients undergoing ambulatory hemodialysis on a regular basis. In most cases, a DA is the preferred long-term or permanent solution (1,2). The majority of DA failures occur due to stenosis or occlusion and can be repaired by percutaneous intervention including PTA and local thrombolysis with initial success rates above 90% and primary patency rates of 23% at 12 months (4,5,12,13). The culprit stenosis that leads to malfunction of AVG can be identified in the anastomosis in half of the patients with prosthetic AVGs. In patients with autogenous AVFs it is more common in the outflow vein. Stenosis in failing AVGs is attributed to intimal hyperplasia due to increased wall shear stress and other mechanisms with secondary thrombosis caused by decreased flow velocity and stasis (3).

Maintaining failing DA is a matter of finding a line between the requirement of repeated percutaneous interventions and surgical correction or a redo procedure (14). Nearly all patients with DA require at least one percutaneous intervention (14). Early resolution of DA stenosis improves the functioning of the circuit, but randomized trials were unable to demonstrate its positive effect on DA survival (15,16). Lessons have been drawn from other vascular interventions, and stents and stent grafts have been tested in DAs in the treatment of stenosis, aneurysms and ruptures initially in off-label settings (17).

A percutaneous approach to DA stenosis by PTA has been long established as the best treatment in most cases and used as the gold standard (14,18,19). The primary patency rates after PTA of DA regardless of location (arm, forearm) vary widely in the literature and are about 25-30% for AVG and 67% for AVF at 1 year (3). Up to 70% of patients require a second intervention within one year (5,20). Secondary patency rates usually with multiple interventions are about 82% at one year and 70% at two years (3,8).

Initial attempts to improve patency rates of AVF by placement of bare stents have been disappointing and their hypothesized advantage over PTA alone did not materialize (21,22). Only nitinol stents showed improved flow in the AVF with and better patency rates with a pooled relative risk of 0.79 (2,6,7). Compared to stainless steel, nitinol (nickel-titanium alloy) stents do not shorten during deployment (23).

Further development based on the promising bare nitinol stent resulted in the design of a covered stent graft that was used in a randomized multicenter trial by Haskal *et al* who compared short-term patency rates in 190 patients with venous anastomotic stenosis in a prosthetic AVG (8). In their study, PTA with the placement of a stent graft showed significant improvement in overall primary patency rates of the AVG and freedom from subsequent interventions at six months compared to PTA alone (32% vs. 16%) (8). The advantage of a stent graft over PTA was later confirmed in other studies as well (9). Carmona *et al* compared primary patency rates in patients with failing grafts due to stenosis at the graft to vein anastomosis between PTA and heparin bonded stent graft and reported improved primary patency rates from 9 to 42% and an increased proportion of functional grafts from 36 and 88% at 12 months (24). Both rival stent grafts (nitinol stents covered with ePTFE), the Viabahn® and Fluency® were compared in a study by Schmelter *et al* (25), who did not prove any difference in primary and secondary patency rates in the treatment of stenosed AVGs and AVFs. In their study, the primary

Table I. Study group characteristics at baseline.

Characteristics	PTA n=20	Stent n=19	Stent graft n=20	P-value
Age	61±17	68±11	65±13	0.30
Sex (women)	15	12	15	0.64
Coronary artery disease	4	4	10	0.087
Chronic heart failure	6	1	3	0.13
Diabetes	9	10	7	0.58
Smoker or ex-smoker	7	8	10	0.64
Arterial hypertension	15	18	17	0.27
Hyperlipoproteinemia	8	13	15	0.061
Therapy				
ACE inhibitor	6	6	9	0.62
Statin	6	6	10	0.40
Antiplatelet	14	17	17	0.34
Anticoagulation	12	10	6	0.14
Vascular access since (years)	3.1 (IQR 3.8)	3.3 (IQR 5.4)	4.0 (IQR 3.0)	0.88
Vascular access type				
Loop	12	13	15	0.61
Straight	8	6	5	
Inflow artery				
Brachial artery	16	15	16	1.0
Radial artery	4	4	4	
Outflow vein				
Superficial vein	13	15	16	0.60
Deep system	7	4	4	

PTA, percutaneous transluminal angioplasty; IQR, interquartile range.

Table II. Vascular access, stenosis, primary and secondary interventions.

Characteristics	PTA n=20	Stent n=19	Stent graft n=20	P-value
Reference diameter (mm)	6 (IQR 1)	6 (IQR 1.5)	6.3 (IQR 1)	0.77
Restenosis location				
Venous arm	11	8	4	0.065
Anastomosis	9	11	16	
Stenosis (%)	66±16	67±16	67±9	0.90
Stenosis after PTA (%)	17±12	9±10	11±10	0.054
Follow-up (months)	22.1 (IQR 4.8)	22.3 (IQR 3.8)	23.6 (IQR 15.1)	0.36
Thrombosis	1 (5%)	3 (16%)	1 (5%)	0.60
Infection	0	0	1 (5%)	1.0
Secondary PTA <1 year	2.8±1.4	2.3±1.8	1.4±2.4	0.015[a]
Secondary PTA <2 years	5.5±2.8	4.8±3.7	3.3±5.1	0.037[b]

PTA, percutaneous transluminal angioplasty; IQR, interquartile range. [a]P<0.01 between PTA and stent graft in a post hoc test, [b]P<0.05 between PTA and stent graft in a post hoc test.

patency rates were 31% at 12 months and 19% at 24 months. Our results with 65 and 37% primary patency rates at 12 and 24 months in the stent graft group and only prosthetic AVGs compare favorably with the results from Schmelter *et al* (25). The success rate of the deployment of stents and stent grafts in our study is comparable to other studies that consistently report high rates near 99% confirming the safety of both approaches (8,25).

Table III. Multivariable Cox proportional hazard regression analysis model for primary patency rates-variables retained in the model (P=.005) and their hazard ratios.

Variables	Hazard ratio	95% CI	P-value
Residual stenosis following initial PTA	1.048	1.013 to 1.084	0.007
Diameter of the reference segment adjacent to the stenosis	0.498	0.306 to 0.813	0.005
Outflow to the superficial venous system vs. deep venous system	0.457	0.233 to 0.894	0.022

PTA, percutaneous transluminal angioplasty; CI, confidence interval.

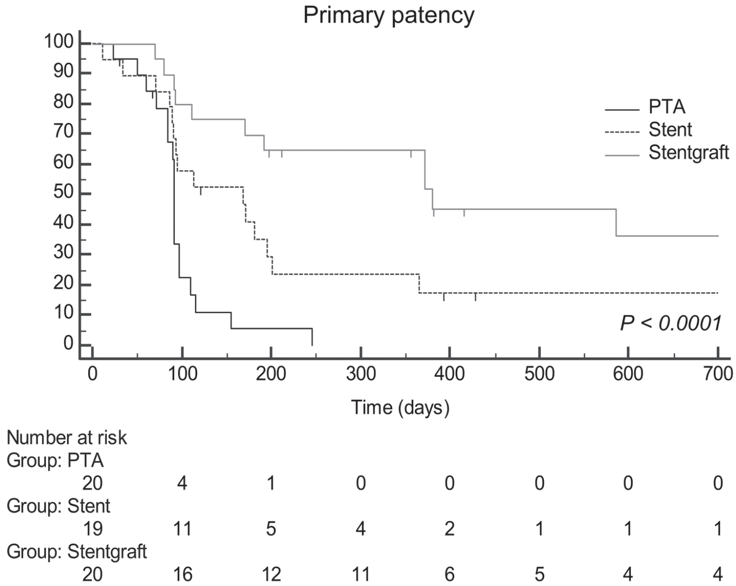

Figure 3. Comparison of primary patency rates among PTA, stent, and stent graft groups in a Kaplan-Meier plot. PTA, percutaneous transluminal angioplasty.

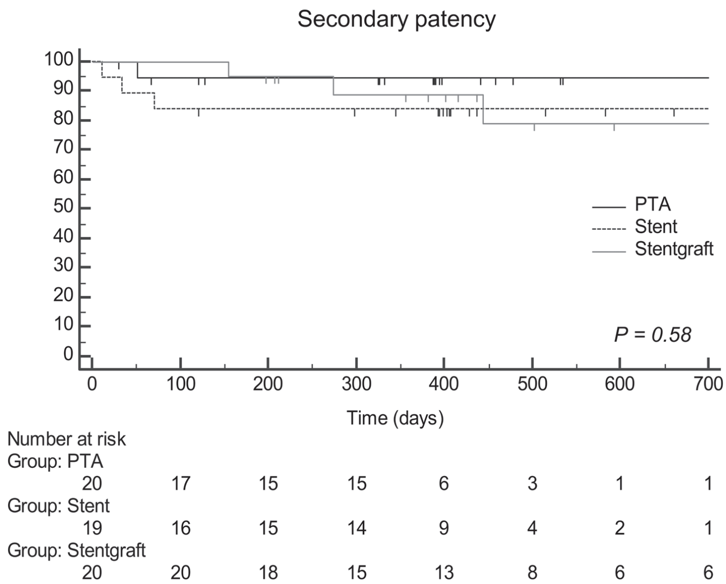

Figure 4. Comparison of secondary patency rates among PTA, stent, and stent graft groups in a Kaplan-Meier plot. PTA, percutaneous transluminal angioplasty.

The effect of antiplatelet agents and their risk to benefit ratio in dialysis patients is poorly understood especially in AVGs and their general use for preventing AVG thrombosis is therefore not recommended due to lack of supporting data (3,26,27). Their use after placement of stent graft in stenosed dialysis access has not been included in the protocol of previous studies and left on the discretion of the referring physician (8,25). In our study, the protocol required dual antiplatelet therapy after deployment of stent or stent graft. We believe that this might have improved their performance compared to the PTA group.

The comparison of primary and secondary patency rates after intervention should be viewed in the perspective of study design. Intensive follow-up programs with tight monitoring of the vascular access and early intervention artificially decrease the primary patency rates (10). Moreover, lower patency rates can be expected in AVGs, younger DA, in the presence of longer lesions, and residual stenosis after PTA (25,28). The present study confirmed that greater residual stenosis after initial PTA is a risk factor and identified further two factors: Smaller diameter of the reference segment adjacent to the stenosis and the use of a deep vein as the outflow.

Numerous approaches to the management of stenosed or malfunctioning DA have also been compared on the cost-effectiveness basis. The debated intensive surveillance program has an incremental net cost for a modest decline in DA thrombosis and is less efficient than increasing the proportion of autogenous fistulas (13,29). The cost-effectiveness of stents and stent grafts in the treatment of DA stenosis has been questioned due to the high cost of the devices and a limited number of randomized studies with long-term endpoints (10). Our study showed that deployment of a stent graft results in decreased number of subsequent PTAs, but the reduction in cost for maintaining AVG patency in our country was not significant. We estimate that in countries such as the USA or India the deployment of a stent graft in this scenario would reduce the cost of maintaining the access from the payer's perspective by a greater margin due to higher ratio between the procedure reimbursement rates and the price of the stent graft, even more than predicted by Dolmatch *et al* (30). Nevertheless, the sole reduction of the number of PTAs can be regarded as a clear benefit to the comfort of the patient.

In conclusion, this study confirms that treatment of failing dialysis vascular access due to restenosis in the anastomosis or the outflow vein by the deployment of a stent graft significantly improves its primary patency rate and decreases the number of secondary PTA interventions in comparison with PTA and deployment of a stent. The cost analysis showed that the reduction in cost for maintaining AVG patency is not statistically significant. The present study confirmed that greater residual stenosis after initial PTA is a risk factor and identified further two: Smaller diameter of the reference segment adjacent to the stenosis and the use of a deep vein as the outflow. Finally, the safety of all three compared approaches was confirmed.

The present study has several limitations. Firstly, the sample size is relatively small. Secondly, the study groups are heterogeneous in term of the location of the restenosis. Thirdly, only one type of stent graft was used. Fourthly, dual antiplatelet therapy was required in the stent and stent graft groups only, but patients from the PTA group received or continued at least one antiplatelet agent or continued their anticoagulation therapy. Lastly, the cost analysis pertains to the author's country.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JKa, JKu, AB and JM conceived and designed the study; JKa, JKu, EC, MS, and PM performed examinations, interventional procedures, and collected the data; JKa, JKu, and LL performed analysis; JKa, JKu, LL, and AB drafted the paper; all authors approved final version of the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, it was approved by the Ethics Committee of the General University Hospital in Prague, and all patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

More precise diagnosis of access stenosis: ultrasonography versus angiography

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ABSTRACT

Purpose: **Patency of mature vascular access for hemodialysis is mostly limited by the growing stenoses leading to acute access thrombosis. The therapy of choice is usually percutaneous balloon angioplasty (PTA). However, PTA injures the vessel wall and subsequent re-stenosis develops faster than de novo stenosis. Therefore, the key is in appropriate timing of PTA procedures – as late as possible but before access thrombosis develops. Ultrasonography combines the morphologic and functional access assessment, but the former is less precise than angiography. The aim of this study was to compare ultrasonographic and angiographic measuring of residual diameter as the additional criterion of significant stenoses used in our center.**

Methods: **Residual diameter of significant stenoses was measured by B-mode ultrasonography three times in 20 patients. All the patients were indicated for angiography and the residual diameter of the stenoses was re-analyzed by this method. The repeatability of ultrasonographic residual diameter measurements and reproducibility in comparison to angiography were expressed by coefficients of variation (CV).**

Results: **The residual diameter was 1.69 ± 0.05 mm by ultrasound and 1.65 ± 0.59 mm measured by angiography. In the ultrasound repeatability study, CV was 3.17 ± 2.76% and in the reproducibility study CV was 18.0 ± 15.6%. All the stenoses found to be significant by ultrasound were above 65% by angiography and PTA was performed.**

Conclusions: **Ultrasonographic measurement of the residual diameter is stable in experienced hands and is well comparable to angiography results. These findings advocate residual diameter of 2.0 mm as the strong additional criterion of the significant stenoses, which can also be used in ultrasound surveillance of arteriovenous grafts.**

Key words: Angiography, Duplex Doppler ultrasound, Hemodialysis vascular access, Residual diameter, Significant stenosis

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INTRODUCTION

The functionality of mature vascular access is mostly limited by developing stenoses on the basis of neointimal hyperplasia (1). In AV fistulas, the most typical site is the outflow vein segment adjacent to the anastomosis. Its development is influenced by the vasodilatory capacity of the vein, surgical technique, and by the jet of blood coming from the feeding artery because of the end of vein to side of artery anastomosis (2). In AV grafts neointimal hyperplasia occurs especially in the venous anastomosis. Wall shear stress abnormalities, mismatch in elastic properties, and reaction to foreign body are among the most frequently suspected reasons (3). Progression of the stenoses leads to reduction in blood flow with higher intradialytic recirculation and risk of access thrombosis (4). Percutaneous transluminal angioplasty (PTA) is the initial therapeutic choice for managing significant stenoses of vascular access (5). It is known that elective PTA has better outcome than the emergent therapy of an already thrombosed access (6). Unfortunately, re-stenoses develop frequently after PTA, which requires repetition of the procedure. The reason is vascular wall injury, which accelerated the neointimal hyperplasia and the restenosis develops faster than a virgin stenosis (7). Therefore, PTA procedures should be correctly indicated (8).

The key is in appropriate timing of PTA procedures. In addition to the physical examination and intra-dialytic hemodynamic monitoring (blood flow volume and venous pressure) (9,10), duplex Doppler ultrasonography (DDU) is a suitable noninvasive and inexpensive method compared with angiography, which is used in vascular access surveillance in some centers. The largest randomized study proving the advantage of DDU surveillance was

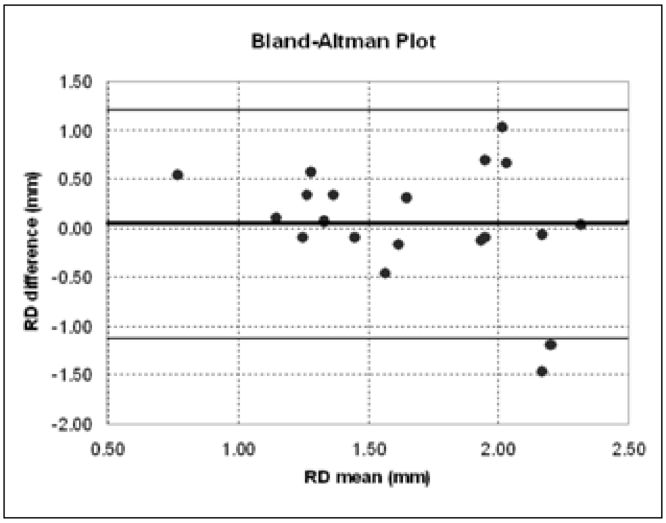

Fig. 1 - *The reproducibility of RD was illustrated using a Bland - Altman plot by RD difference (RD mean measured by DDU minus RD measured by angiography) versus RD mean (DDU). A solid horizontal line shows the mean RD difference (so-called systematic error), thin lines limits of agreement (mean RD difference ± 1.96 x coefficient of variation).*

performed in our center (11). The results have been discussed (12) because other studies (13-15) did not prove the benefit of DDU surveillance. According to our opinion, our positive results could be accounted for at least in part by the strict definition criteria of the significant stenosis. In other words, it seems to be reasonable to perform PTA as late as possible, but before access thrombosis develops.

We use the concept of the borderline stenosis (see Methods for definition) in the randomized trial and in two other subsequent smaller trials (16,17). When the borderline stenosis is found, we indicate DDU control sooner, while in case of the significant stenosis early PTA procedure is suggested. It has been proven that AV grafts with stable borderline stenoses have a low risk of thrombosis.

In addition to measuring the percentage of lumen reduction and flow velocity increase, we started to use the residual diameter (RD) of the stenotic lumen. RD equal to or below 2.0 millimeters was used as the additional criterion of significant stenoses. However, ultrasound examination is thought to be highly variable especially under less-than-ideal conditions. No comparison of DDU and angiographic RD measurements has been performed yet. Therefore, the aim of this study was to support our concept of strict definition of significant stenoses by measuring the accuracy of ultrasound estimation of residual diameter. We determined the reproducibility and repeatability of RD measurements in significant stenoses by DDU compared with angiography as the golden standard method, followed by estimation of degree of stenoses.

MATERIALS AND METHODS

Participants of this study were patients of the Vascular Access Center in the General University Hospital in Prague, Czech Republic, which provides care for >50 dialysis units. For the purpose of this study we selected 20 patients with significant stenosis (see below for definition) diagnosed by DDU in any of the following: feeding artery, graft with the venous anastomosis of AV grafts or outflow vein.

All vascular access parts were checked up by B-mode and color Doppler mapping. When a stenosis was suspected (aliasing in color Doppler mapping and/or narrowing in B-mode), residual diameter (RD) was measured three-times and systolic velocities in the stenotic and pre-stenotic regions were recorded to calculate peak systolic velocity ratios (PSR). PSR was defined as the ratio of the peak velocity inside the stenosis and the peak velocity in an adjacent unaffected pre-stenotic segment. The DDU examination also included estimation of the vascular access flow calculated as the lumen cross-section multiplied by time-averaged mean velocity. In case of AV grafts, the access flow was measured in the venous part of the graft at least 2 cm before the venous anastomosis or in the brachial artery in case of native AV fistulas. All examinations were performed using the VIVID 7 device with 11 MHz linear array probe (General Electrics, USA).

The stenosis was found to be significant if there was a combination of >50% lumen reduction in B-mode and PSR >2, together with at least one of the following additional criteria: (1) residual diameter <2.0 mm and/or (2) low blood flow (<600 mL/min) or blood flow reduction of >25% since the previous examination. Stenoses without any additional criterion were considered borderline and DDU control within 10 weeks was indicated. Patients with significant stenoses were indicated for angiography and PTA procedures were performed. Digital subtraction angiography was performed using a non-ionic contrast agent on the Siemens Axiom Artis MP device. Stenoses >50% on angiography were indicated for PTA with the attempt to obtain an angiographically optimal result.

Residual diameter was separately measured and collected by a skilled ultrasonographist and by a skilled invasive radiologist. Ultrasonographic analysis of RD was performed using built-in calipers of the ultrasound device. Angiographic measurements were taken semi-automatically after appropriate scaling. The angiographist was blinded with respect to the ultrasound results. We performed the repeatability study (i.e. intra-reader repeatability of ultrasonographer, based on three measurements of RD) and the reproducibility study (i.e. comparison of mean RD ascertained by DDU and by angiography). The variability of the results was expressed by coefficient of variation (CV) in both studies. CV was calculated using the formula:

$$CV = \frac{3}{x}\sqrt{\frac{3}{N-3}\sum_{i=3}^{N}\left(x_i - \bar{x}\right)^4}$$

i.e. sample standard deviation divided by the mean. For the ultrasound repeatability study $\bar{x}$ is mean RD ascertained by DDU, x_i are RD values, and *N* is number of measurements (three in this case). For the reproducibility study $\bar{x}$ represents mean of RD ascertained by angiography and the mean RD ascertained by DDU, x_i are angiographic and ultrasonographic RD values, and *N* is equal to two in this case. Repeatability and reproducibility were expressed as mean CV ± SD of CV.

RESULTS

We included 20 patients (aged 69 ± 8 years) with hemodynamically significant stenoses of the vascular accesses according to the aforementioned criteria diagnosed by DDU. All patients had subsequent angiography, which proved the significant stenoses (above 65%) in all cases and the patients were treated by PTA. Types of accesses and locations of stenoses are reported in Table I.

The mean RD measured by DDU and DSA was 1.69 ± 0.05 mm and 1.65 ± 0.59 mm, respectively. CV was 3.88 ± 3.38% in the ultrasound repeatability study and 18.0 ± 15.6% in the reproducibility study. Thirteen out of 15 stenoses with the additional criterion RD <2.0 mm (the narrowest) were considered >85% by angiography. The remaining two were overestimated by DDU (1.4 vs. 2.9 mm and 1.6 vs. 2.8 mm, respectively) because of bad visual clarity at the site of the stenosis caused by calcifications, but were still hemodynamically significant. The reproducibility study was mainly affected by these measurement errors in five patients (with reproducibility >30%). Repeatability of measuring RD by one investigator was surprisingly low according to variations in the order of tenths of millimeters.

The Bland-Altman plot shows that the variation of DDU results compared to angiography depends on the actual residual diameter size (Fig. 1).

TABLE I - TYPES OF ACCESSES AND LOCATIONS OF STENOSES

Type of access	Number
AVF	5
AVG	15
Stenosis location	
venous anastomosis	6
outflow vein	10
PTFE graft	3
feeding artery	1

AVF, arteriovenous fistula; AVG, arteriovenous graft; PTFE, polytetrafluoroethylene
The proportion of access types corresponds to the spectrum of patients screened in our centre (about 75-85% of them have PTFE grafts). The most frequent stenotic lesions were found in the venous anastomosis as assumed.

DISCUSSION

This study has shown that the DDU measurement of RD is stable in experienced hands and is well comparable to the results of DSA. The measurement of residual diameter by DDU is precise as well as the other criteria of hemodynamically significant stenoses, because all the access stenoses of the selected patients were considered as hemodynamically significant by angiography and PTA was indicated. These findings advocate RD 2.0 mm as a strong additional criterion of the significant stenosis.

It is known that the measurement of RD by DDU could be imprecise either when capturing an incorrect section plane in the 2D image mode or because of worse native visibility caused by calcifications (18,19). Magnification (zoom) or measuring the *vena contracta* in color flow mapping mode could help in these cases. Moreover, the distances measured are very short and the boundary between the lumen and the neointimal hyperplasia especially in the anterior wall is not always clear. According to our results, the wider mean RD measured by DDU can be explained by missing the narrowest site of the stenoses. This implies that DDU examination does not lead to overestimation of RD, which could be a false reason for PTA indication.

The "watch and wait" strategy (20), which is being used for the follow-up of borderline stenoses of AV grafts in our center, is based on their functional quantification including peak systolic velocities and their changes inside the stenosis. Blood flow and its decline are other important criteria we use because they document the function of the access. These hemodynamic parameters are even more important when the morphology of the stenosis is badly readable in native 2D imaging. All this complex information enable us to indicate PTA in time. In a previous study (17) we have shown that delaying PTA of borderline stenoses is safe with only 1% risk of access thrombosis.

Some (13,14) studies and subsequent meta-analysis (15) have not proven the benefit of vascular access ultrasound surveillance programmes. Allon (13) concludes that none of the currently available surveillance tests can reliably distinguish between stenosed grafts destined to clot and those that will remain patent without intervention. However, the trials included in the meta-analysis used various definitions of significant access stenosis (some other trials (21,22) that failed to prove the profit had a 50% reduction in diameter as the only criterion of the significant stenosis), differed as to vascular access age at inclusion, etc (12).

Ultrasound in contrast to regular flow monitoring during hemodialysis provides more complex information about the access. Several limitations of single regular access flow monitoring were published. The mathematic model by Paulson et al (23) using luminal diameters shows that when the stenosis progresses, flow initially remains unchanged but then rapidly decreases. This can account for why some surveillance programmes predict thrombosis in some patients but not in others. Moreover, access flow fluctuates during a long-term follow-up period. Valek et al. (24) studied the physiologic access flow variations and found that its decrease by 20-25% could still be within physiologic limits and access flow variability measured by CV attained 23.3 ± 11.2%. According to Schild, (25), newer grafts are most likely to thrombose, whereas older grafts are unlikely to thrombose even during low flows or large decreases in flow, but more than half the thromboses lacked a change in flow measurement.

We believe that the definition of precise criteria of the significance of stenoses is necessary for the benefit of ultrasound surveillance. Surveillance outcomes might be improved by setting-up strict criteria using both ultrasound modalities: Doppler characteristics of local hemodynamic conditions and the morphologic assessment and soon DDU re-examination must be performed for borderline stenoses. However, only a multicenter randomized trial can definitively answer the question of whether DDU graft surveillance really prolongs access patency.

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Conflict of interest: None to declare.

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