Reinforced Aneurysmorrhaphy for True Aneurysmal Haemodialysis Vascular Access

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WHAT THIS PAPER ADDS

This paper presents the largest series of patients with true venous aneurysm of an arteriovenous fistula. Reinforced aneurysmorrhaphy with external mesh prosthesis is an effective method suitable for surgical treatment of symptomatic true aneurysmal haemodialysis arteriovenous access, with an excellent patency rate, minimal infection rate, and no aneurysmal recurrence. It is appropriate for patients with high-flow aneurysmal fistula.

Objective: In 2008, a new technique of reinforced aneurysmorrhaphy with a polyester mesh tube for salvaging true aneurysmal arteriovenous (AV) haemodialysis access was described by us. In this study, the long-term patency and complication rates associated with this procedure were analysed, and the effect of reinforced aneurysmorrhaphy on high-flow vascular access was assessed.

Methods: This was a retrospective non-randomised study with prospectively collected data performed at a single centre. Patients with true aneurysmal haemodialysis AV access who underwent aneurysmorrhaphy with external mesh prosthesis between March 2007 and October 2012 were included. Clinical assessment and duplex ultrasound were performed preoperatively, 1, 3, and 12 months postoperatively, and annually thereafter.

Results: Data from 62 patients (median age 60 years, range 28—81 years; 63% men) were analysed. The commonest indication was high-flow vascular access associated with the risk of high output cardiac failure (24 patients, 39%). The mean follow-up time was 14.66 ± 12.80 months. Primary patency rates at 6 and 12 months were 86% and 79% respectively. Assisted primary patency rates at 6 and 12 months were 89% and 80% respectively. In 23 patients (96%) operated on for high-flow vascular access, decreased vascular access flow was observed after the procedure. The average flow reduction after aneurysmorrhaphy was 2,197 mL/minute. Postoperative bleeding and infection necessitating surgical revision occurred in three (4.8%) and three (4.8%) patients respectively.

Conclusions: Reinforced aneurysmorrhaphy with an external mesh prosthesis is an effective method for treating true aneurysmal haemodialysis AV access, with excellent long-term patency and minimal complications due to infection.

Article history: Received 3 September 2013, Accepted 13 January 2014, Available online 21 January 2014
Keywords: Aneurysm, Aneurysmorrhaphy, Arteriovenous access, External mesh prosthesis, High-flow access

INTRODUCTION

The incidence of true venous aneurysm formation in a haemodialysis arteriovenous fistula (AVF) is reported to be as high as 30%.[1] The clinical presentation of aneurysm is often asymptomatic, does not require any intervention, and can be managed by abandoning cannulation.[2] Treatment is indicated in cases of symptomatic aneurysm presenting with active bleeding, imminent risk of rupture, fistula infection, excessive fistula blood flow, or significant cosmetic issues.[3] Although several types of surgical and endovascular procedures have been described, clinical guidelines are limited in terms of when and how to intervene.[2,4] In 2008, a new technique for salvaging a true aneurysmal AVF by reinforced aneurysmorrhaphy with a mesh tube was described by us.[5] In this report, data on

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1078-5884/$ — see front matter
http://dx.doi.org/10.1016/j.ejvs.2014.01.010

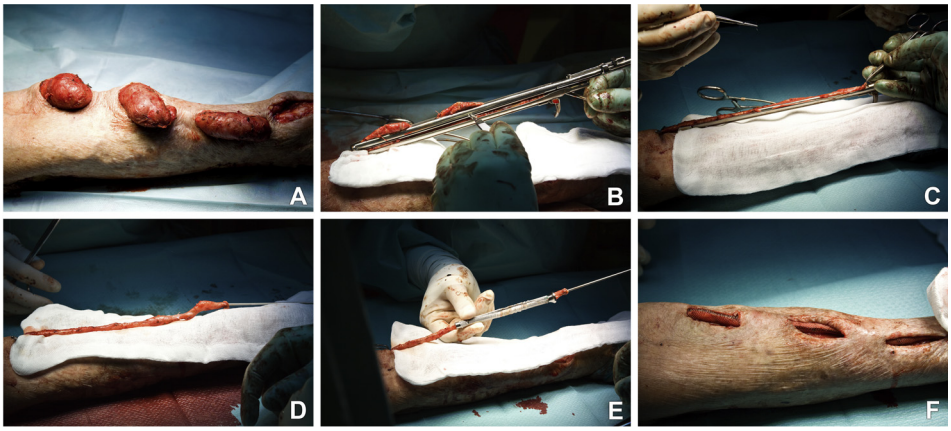


Figure 1. Reinforced aneurysmorrhaphy technique. (A) Venous arm of the fistula mobilised up to the non-dilated part of the vein; (B) resection of aneurysms using BalRok clamp; (C) vein wall remaining after aneurysm resection sewn with a continuous running suture; (D) repaired vein after aneurysmorrhaphy; (E) implantation of external mesh prosthesis; (F) repaired vein tunnelled subcutaneously and re-anastomosis.

long-term patency and complication rates with this technique are presented, and the effect of this technique on high-flow vascular access is assessed.

MATERIAL AND METHODS

Study population

Between March 2007 and October 2012 this department treated 551 patients for arteriovenous (AV) access creation or AV access complications, including patients with true aneurysmal AVF. Demographics, pre- and perioperative, and follow-up data were recorded prospectively in an institution database. Patients with true aneurysmal haemodialysis AVF who had been treated by reinforced aneurysmorrhaphy were identified. The case records were analysed retrospectively. Informed consent was obtained from all patients preoperatively.

Preoperative assessment

Duplex ultrasound was used to assess the diameter and length of the aneurysm, the presence of intraluminal thrombus and stenosis, the blood flow in the brachial artery, and the size of the AV anastomosis, and to exclude the possibility of central vein stenosis. When central vein stenosis was suspected, fistulography was performed. Patients with high-flow access (defined as flow in the brachial artery $>$2,500 mL/minute) were referred for cardiology examination to assess the presence of hyperkinetic circulation. Hyperkinetic circulation was defined as a cardiac index of more than 3.9 L/minute/m^2, measured by transthoracic echocardiography. High output cardiac failure was defined as a combination of hyperkinetic circulation with the physical findings of systemic venous or pulmonary congestion.[6] All patients with an aneurysmal AVF with chronic kidney disease (CKD) stage 1—3 at the time of the study who had had a previous renal transplant (AVF was created prior to renal transplant) were treated by AVF ligation and creation of new access at the time of the deterioration. However, the definitive indication for the salvage of the AVF was always discussed with nephrologists in all patients, and the actual renal function and the status of the kidney transplant (the history of rejection and delayed graft function with the type of organ donor) was considered. If the risk of deterioration of renal function was considered high, salvage of the AVF by aneurysmorrhaphy was indicated.

Reinforced aneurysmorrhaphy technique

All procedures were performed by two surgeons. Patients were given general or locoregional anaesthesia. Intravenous prophylactic antibiotics (cefazolin 1 g) were administered 30 minutes before surgery. Small skin incisions (3—5 cm) were made at the site of the AV anastomosis. Another incision (3—5 cm) was made along the whole length of the aneurysmal vein.

The anastomosis was dissected, and the aneurysmal fistula vein was mobilised up to the non-dilated part (Fig. 1A). Heparin (5,000—10,000 IU) was administered. The supplying artery and non-dilated vein above the proximal aneurysm were clamped. Immediately beyond the AV anastomosis, the vein was disconnected from the artery, and the aneurysmal sacs were resected (Fig. 1B). To resect the aneurysmal vein, a metal tube (5, 6, or 7 mm in diameter) was inserted into the vein. The vein wall remaining after aneurysm resection was sewn with a continuous running suture (Fig. 1C,D). From February 2011 onward, aneurysms were resected using a special instrument developed by our team, called the BalRok clamp.[7]

The repaired vein was scaffolded with an external mesh prosthesis (ProVena, BBraun Medical, Melsungen, Germany) with a diameter 1 mm larger than the metal tube of the BalRok clamp (Fig. 1E). The meshed vein was tunnelled subcutaneously to the previous anastomosis site, and re-anastomosis was performed (Fig. 1F). Heparin was neutralised by an adequate dose of protamine sulphate and, upon checking haemostasis, two Redon drains were placed before wound closure. In the postoperative period, all patients were administered 100 mg of acetylsalicylic acid.

Table 1. Patient characteristics.

Variable	*n* (%) or median (range)
Demography	
Age (y)	60 (28–81)
Men	39 (63)
Hypertension	57 (92)
Diabetes	10 (16)
Tobacco use	14 (23)
Coronary artery disease	6 (10)
Stroke/TIA	2 (3)
Peripheral arterial disease	1.0 (1.5)
Previous renal transplantation	46 (74)
Underlying renal disease	
Glomerulonephritis	24 (39)
Polycystic kidney	13 (21)
Tubulointerstitial nephritis	11 (18)
Renal vascular disease	10 (16)
Unknown	3.0 (4.5)
Diabetic nephropathy	1.0 (1.5)
CKD stage	
1	1.0 (1.5)
2	13 (21)
3	22 (35)
4	7 (11)
5	19 (30)

Note. TIA = transient ischaemic attack; CKD = chronic kidney disease.

Postoperative follow-up

Clinical assessment with duplex ultrasound for evaluation of patency and access flow was performed at 1, 3, and 12 months postoperatively and yearly thereafter. Patients with persistent high flow postoperatively were investigated every 3 months. In the case of stenosis or inadequate flow, fistulography was performed.

Endpoints and definitions

The primary endpoint was primary patency rate after aneurysmorrhaphy. Secondary endpoints included assisted primary and secondary patency, procedure-related complications, and the effect of aneurysmorrhaphy in high-flow AVF. In this report, patency is presented according to the recommended standards for reporting AV haemodialysis accesses.[8] An aneurysmal AVF was defined as dilatation having a threefold larger diameter than the vessel segments immediately upstream and downstream from the access site.[16] Technical success was defined by the presence of thrill at the end of the procedure. Stenosis was defined as a more than 50% reduction in diameter, as proven by ultrasound[9] or fistulography. Failed AVF due to thrombosis was detected by clinical assessment and ultrasound. Low and high flow were defined as $<$400 mL/minute and $>$2,500 mL/minute respectively.

Table 2. The influence of various risk factors on primary patency rates.

Variable	Odds ratio (95% CI)	*p*
Age	1.02 (0.99–1.05)	.15
Women	1.15 (0.62–2.15)	.67
Hypertension	1.12 (0.27–4.69)	.88
Diabetes	1.04 (0.45–2.37)	.93
Tobacco use	0.52 (0.22–1.25)	.14
Coronary artery disease	1.92 (0.99–3.74)	.06
Peripheral arterial disease	1.79 (0.89–3.60)	.1

Note. CI = confidence interval.

Statistical analysis

Descriptive statistics are expressed as the mean ± SD, median (interquartile range [IQR]) or frequency (%). The effect of the operation on flow was assessed using the paired *t* test. Categorical variables were compared using the chi-square test. Patency analyses were performed using the Kaplan–Meier method. Differences between groups were determined with the log-rank test. A Cox proportional hazards model was used to assess the influence of different parameters on patency. Calculations were done using SPSS version 20 (IBM, Somers, NY, USA). A two-sided *p*-value $\leq$0.05 was considered statistically significant.

RESULTS

During the study period, 62 patients were treated, including 39 men (63%), with a median age of 60 years (range 28–81 years). Other patient characteristics are shown in Table 1. Hypertension and diabetes were present in 57 (92%) and 10 (16%) patients respectively. In the multivariate analysis, these risk factors did not affect the patency rate (Table 2). Forty AVFs (65%) were in the forearm, and the other 22 AVFs (35%) were in the upper arm. Other AVF characteristics are shown in Table 3. Indication for treatment was the presence of true multiple (concomitant) AVF aneurysms associated with another indication (Table 3). The most common additional indication was high-flow AVF (24 patients, 39%), with a mean flow rate of 3,968.4 ± 1,923.8 mL/minute. Two patients had chronic heart failure due to hyperkinetic circulation, as diagnosed by a cardiologist, despite having AVF volume flows of 1,600 and 1,800 mL/minute respectively.

The mean operative time was 138 ± 37 (80–240) minutes. The diameter of the external mesh prosthesis used was 6 mm in nine patients (14%), 7 mm in 45 patients (73%), and 8 mm in eight patients (13%). The BalRok clamp was used in 37 patients (60%). Technical success was obtained in all patients, with a median postoperative hospital stay of 3 (1–23) days. In patients on haemodialysis, median time to use of the AVF was 4 weeks. The mean follow-up time was 14.6 ± 12.8 (0–67) months, and follow-up was completed by all patients.

The primary patency rates at 6 and 12 months were 86% and 79% respectively. Two patients required percutaneous angioplasty of central vein stenosis; however, the vein lesions were not related to the part of the vein that had undergone aneurysmorrhaphy. Six patients (9.6%) underwent angioplasty for stenosis of the vein after aneurysmorrhaphy, with immediate technical success. One

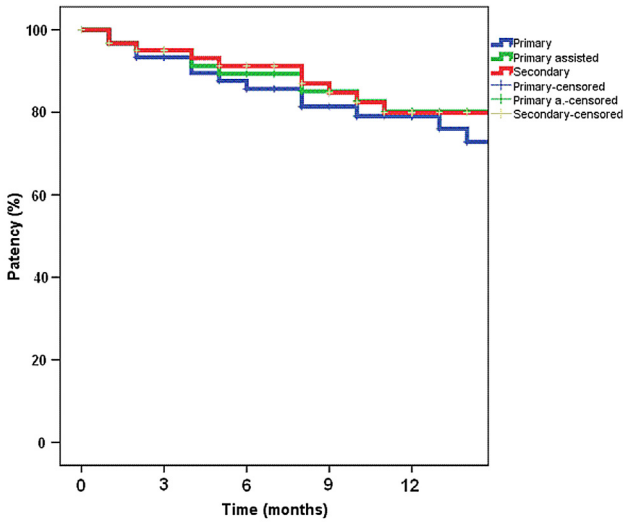
patient required reoperation for AVF malfunction owing to occlusion of the ulnar artery. Repositioning of the anastomosis was performed at 16 months postoperatively. Assisted primary patency rates at 6 and 12 months were 89% and 80% respectively. Two late AVF thrombosis events in one patient, which occurred at 4 and 8 months postoperatively, were managed surgically. Secondary patency rates at 6 and 12 months were 91% and 80% respectively. Kaplan–Meier curves for patency rates are shown in Fig. 2. Patency rates did not differ between forearm and upper arm operations ($p = .50$).

In 24 patients (39%), aneurysmorrhaphy was performed for high-flow AVF. In all but one of these patients flow through the AVF was significantly decreased after the operation (3,968.4 ± 1,923.8 mL/minute before vs. 1,771.1 ± 843.4 mL/minute after operation, $p < .001$). The mean flow reduction was 2,197 mL/minute (Fig. 3). Two patients with high-flow fistulae underwent reoperation for an inadequate reduction in flow. In the first patient, flow decreased by >4,500 mL/minute, but it increased during the follow-up period of 9 months to the preoperative value (6,000 mL/minute). Reduction of the anastomosis was performed 11 months after the primary operation. Postoperatively, flow decreased again, but during the next 9 months it increased to >2,500 mL/minute. The patient was in CKD stage 2. Because of signs of cardiac failure, ligation was performed 21 months after the primary surgery. In the second patient, flow decreased postoperatively >1,000 mL/minute; however, the flow rate remained >2,500 mL/minute. This patient was successfully treated 13 months after the primary surgery by a further reduction of the anastomosis.

Postoperative bleeding necessitating surgical revision occurred in three patients (4.8%). Infection of the prosthesis (with *Staphylococcus aureus*) occurred in one patient 30 days after surgery. Explantation of the AVF was performed. One patient developed a phlegmon 1 week after surgery; antibiotics were administered, with improvement of the condition. Thrombosis of the AVF with concomitant phlegmon and pain then developed 2 months postoperatively; conservative treatment was unsuccessful, and AVF resection with mesh removal was performed 3 months after the primary surgery (culture findings negative). Another patient developed small necrotic skin lesions overlaying the AVF with mesh exposure 3 months after surgery (culture findings were negative). In this case, the AVF was resected and

Table 3. Arteriovenous fistula (AVF) characteristics and surgical indications.

Variable	*n* (%)
Type of AVF	
Forearm	
Radial-cephalic fistula	39 (63)
Ulnar-cephalic fistula	1 (2)
Upper arm	
Brachial-cephalic fistula	15 (24)
Brachial-basilic fistula	7 (11)
AVF characteristics	**Mean ± SD (range)**
Number of aneurysms	2.33 ± 0.57 (1.00–3.00)
Maximum aneurysm diameter (mm)	34.47 ± 7.33 (20.00–55.00)
AVF survival (y)	9.03 ± 6.07 (2.00–29.00)
Indication	***n* (%)**
High-flow AVF	24 (39)
Pain overlaying skin	15 (24)
Progressive enlargement	12 (19)
Bleeding	5 (8)
Steal syndrome	3.0 (4.5)
Stenosis	2 (3)
Thrombosis	1.0 (1.5)



Time (months)	0	1	3	6	9	12
Primary (*n* of patients)	62	57	49	42	35	26
Primary patency (%)	100	97	93	86	81	79
Primary a. (*n* of patients)	62	57	50	44	36	26
Primary a. patency (%)	100	97	95	89	85	80
Secondary (*n* of patients)	62	57	50	45	36	26
Secondary patency (%)	100	97	95	91	85	80

Figure 2. Kaplan–Meier curve showing primary, primary assisted, and secondary patency rates after aneurysmorrhaphy.

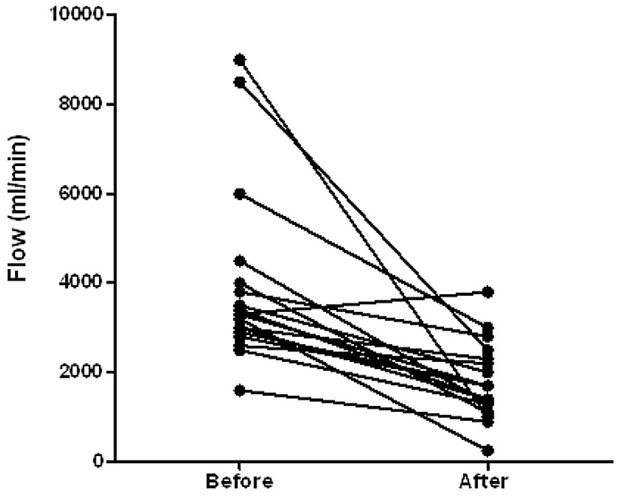


Figure 3. Arteriovenous fistula (AVF) flow rate before and after aneurysmorrhaphy in the subgroup of patients with high-flow AVF.

Table 4. Postoperative complications.

Variable	*n* (%) <30 d	*n* (%) ≥30 d	*n* (%) Total
Haematoma without revision	7 (11)	0	7 (11)
Bleeding with revision	3.0 (4.5)	0	3.0 (4.5)
Infection of prosthesis	1.0 (1.5)	2 (3)	3.0 (4.5)
Re-operation for high flow	0	2 (3)	2 (3)
Non-fatal cardiac	0	2 (3)	2 (3)
Stoke/TIA	0	1.0 (1.5)	1.0 (1.5)
Death	1.0 (1.5)	7.0 (11)	8.0 (12.5)

Note. TIA = transient ischaemic attack.

a new AVF was performed in the same session. Although the culture findings were negative in these two cases, both contributed to the infectious complication rate (three patients, 4.8%).

There was one perioperative and there were eight late deaths that were unrelated to the aneurysmorrhaphy procedure. Complications are listed in Table 4. During follow-up (14.66 ± 12.80 months) we did not record any recurrence of aneurysm of the AVF.

DISCUSSION

Although autogenous AV access for haemodialysis is a routine surgical procedure, the long-term patency is limited, aneurysmal enlargement is not uncommon, and complications can be severe. AV access increases cardiac output, which may lead to eccentric left ventricular hypertrophy, which is a key factor in the development of congestive heart failure in haemodialysis patients.[6] While the exact pathogenesis of aneurysmal dilatation remains unclear, several mechanisms have been proposed. Frequently discussed are the effects of repeat needle puncture for dialysis,[10] haemodynamic factors, such as pre- and post-aneurysm stenotic lesions,[2] and the effects of hypertension or immunosuppression.[11]

The KDOQI vascular access guidelines recommend that uncomplicated aneurysms be managed by abandoning cannulation of the aneurysmal areas in favour of healthier fistula segments.[2] Recently, the buttonhole technique was recommended as a method to reduce existing aneurysm enlargement.[12] Numerous case reports and small case-series of aneurysmal AVF treatment have been published. Several techniques have been proposed, including aneurysm resection with/without graft interposition,[13–14] partial aneurysmectomy,[3] plication, venorrhaphy with stapler,[15] aneurysmorrhaphy with/without mesh prosthesis or metal mesh,[5,16,17] endografting,[18] and ligation. However, there are no randomised controlled trials comparing these methods. It has been proposed that the implantation of an external mesh prosthesis on the surface of the vein to be repaired decreases the venous wall shear stress, thereby decreasing the turbulent blood flow, endothelial damage, and mural thrombus formation.[19,20]

The aims of this study were to analyse the long-term patency and complication rates in a cohort of 62 patients who underwent reinforced aneurysmorrhaphy with an external mesh prosthesis, and to evaluate the effect of this method in patients with high-flow fistulas. The assisted primary patency of our technique (80% at 12 months) is comparable to the assisted primary patency reported by Berard et al. (93% at 12 months),[16] who tested our method in 33 patients. Woo et al.[21] performed aneurysmorrhaphy without an external mesh prosthesis in 19 patients, with a median follow-up of 23 months (IQR 22 months). They observed a median primary patency of 14 months (IQR 24 at 12 months). The effect of the external support of the weakened vein after aneurysmorrhaphy for maintaining the patency is not clear, and more comparative studies are needed.

Other studies have used techniques other than aneurysmorrhaphy for treating true aneurysmal AVFs. In a study by Pasklinsky et al.,[13] 10 AVF aneurysms were treated. Seven patients were treated by excision and repair with the great saphenous vein, and three patients with excision and repair with prosthetic material. The median follow-up was 19 months, and the primary patency rate at 12 months was 46.7%. Georgiadis et al.[14] included 44 true and false vascular access-related aneurysms in their study (26 in AV fistulas and 18 in AV grafts). Most of these patients underwent resection of the aneurysm and interposition with graft placement. The primary patency rates of the 26 AVFs were 85% and 69% at 6 and 12 months respectively.

Almehmi and Wang[3] treated 36 patients by partial aneurysmorrhaphy, reporting an assisted primary patency rate of 97% at 6 months; however, their mean follow-up time was only 7.1 ± 4.8 months. Shemesh et al.[18] described the use of stent grafts to treat nine graft access pseudoaneurysms and 11 native vein access aneurysms and pseudoaneurysms, with a functional patency rate of 87% at 12 months and median follow-up of 15 (6.3—55.5) months. Although their patency rate is comparable to those reported here, patients with steal syndrome, aneurysms close to the anastomosis, and large aneurysms lacking the stent graft seal zone were excluded. Furthermore, Shemesh did not identify patients with high-flow AVFs. Other remodelling salvage techniques described in the literature include plication and lateral venorrhaphy with stapler.[15,11] Unfortunately, the numbers in these studies are small, the follow-ups are short, and the patency and complication rates are not described clearly.

The great benefit of the present study is the inclusion of a large number of patients with high-flow aneurysmal AVFs (access flow >2,500 mL/minute). We confirmed the effect of reinforced aneurysmorrhaphy on flow reduction in these patients, with flow decreasing from 3,968.4 ± 1,923.8 mL/minute before to 1,771.10 ± 843.49 mL/minute after surgery ($p < .001$). Only one previous study[16] has proven the effect of aneurysmorrhaphy on patients ($n = 16$) with high-flow AVFs (flow rate >1,500 mL/minute). However, in patients with flow >2,500 mL/minute, the effect was not achieved and aneurysmorrhaphy cannot be recommended for this group of patients. For a fistula with flow >2,500 mL/minute located in the forearm, proximal radial artery ligation and end-to-end anastomosis between the repaired

vein and the distal radial artery (if the ulnar artery is patent) is recommended. For upper-arm high-flow AVF, moving the arterial inflow to the forearm artery is recommended.[16]

In this series, only two patients needed reoperation for repeated high-flow AVF. Both cases (one brachiocephalic and one brachiobasilic AVF) presented with brachial artery dilatation. The primary treatment was aneurysmorrhaphy without reduction of the anastomosis. Based on our preliminary results in patients treated for high-flow AVF with aneurysmorrhaphy in the first half of this study, including the two patients who underwent reoperation, the policy has been changed. Aneurysmorrhaphy with anastomosis relocation to forearm arteries in cases with upper-arm high-flow AVF, and aneurysmorrhaphy with reduction of the anastomosis in forearm high-flow AVF are now recommended. Radial artery ligation is never used. Furthermore, it is speculated that brachial artery dilatation is an important risk factor for re-increased flow in the postoperative period.

Although the procedures were registered prospectively in a database, the analysis of the outcome was retrospective, which is a limitation of this study. There are several advantages and limitations of reinforced aneurysmorrhaphy with external mesh prosthesis. Using this technique, it is possible to treat AVFs with multiple (concomitant) extensive aneurysms. The mean maximum aneurysm diameter was 34.47 $\pm$ 7.33 (20—55) mm, and mean number of aneurysms was 2.33 $\pm$ 0.57 (1—3). There were no aneurysmal recurrences during follow-up. There were no recorded difficulties with cannulation of the reinforced vein area or any mesh complications. The procedure was well-tolerated, required minimal hospitalisation, and accomplished desirable cosmetic effect. The main disadvantage is the need for a temporary tunnelled catheter because of the extensive nature of the reconstructive aneurysmorrhaphy procedure. Therefore, cannulation of the repaired fistulae is interrupted for 4 weeks. It is assumed that this time period was too short for central vein stenosis or catheter infection to develop, and no complication associated with use of the temporary central vein catheter was recorded. In patients treated by aneurysmorrhaphy for solitary aneurysm, the haemodialysis should be performed by cannulation of the non-dilated part of the vein above the aneurysmorrhaphy segment. Infection related to the use of prosthetic material was not seen in this study. Infection occurred in three patients (4.8%), and only one of these was confirmed by microbiology. Compared to the study by Woo et al.,[21] who used a similar technique but without external mesh prosthesis, the rate of infection was lower in this series (4.8% vs. 10.5%).

It is believed that this report contains the largest series of patients with true aneurysm fistula or high-flow aneurysm AVF. It is concluded that reinforced aneurysmorrhaphy with external mesh prosthesis is an effective method for treating true aneurysmal AVF, showing excellent long-term patency, no aneurysmal recurrence, and a minimal infection rate. This method appears to be suitable for high-flow AVF. Aneurysmorrhaphy with external mesh prosthesis is recommended as a first-line choice for the management of extensive multiple true aneurysmal AVFs.

ACKNOWLEDGEMENTS

We thank Prof. Martin Björck for reviewing the manuscript.

CONFLICT OF INTEREST

The BalRok clamp is registered in the Office for Harmonization in the Internal Market (OHIM) Trade Marks and Designs — Community Design, RCD application number: 002024539.

FUNDING

None.

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Hypertension Research (2016), 1–6

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ORIGINAL ARTICLE

Cardiac remodeling after reduction of high-flow arteriovenous fistulas in end-stage renal disease

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In patients with end-stage renal disease, excessive blood flow through an arteriovenous fistula (AVF) may lead to volume overload-induced cardiac remodeling and heart failure. It is unclear which patients with hyperfunctional AVF may benefit from AVF reduction or ligation. The indication for the procedure is often based on AVF flow. Because cardiac remodeling is driven by increased venous return, which is equivalent to cardiac output, we hypothesized that an elevated cardiac index (CI) might better identify subjects with reverse remodeling after AVF reduction. Thirty patients (age 52 ± 12 years, 73% male) with AVF flow ⩾ 1.5 l min^{-1} underwent comprehensive echocardiographic evaluations before and after AVF reduction. At baseline, 16 patients had a normal CI (2.5–3.8 l min^{-1} m^{-2}) and 14 had a high CI (4.0–6.0 l min^{-1} m^{-2}). A left ventricular end-diastolic diameter decrease after operation was predicted by elevated baseline CI ($P<0.01$), but not elevated AVF flow ($P=0.07$). There was a significant decrease in CI, left ventricular mass, left atrial and right ventricular diameter and pulmonary systolic pressure in the high CI group but not in the normal CI group. After AVF reduction, systemic vascular resistance decreased in the normal CI group, whereas it did not change in the high CI group. In conclusion, reduction of high-flow AVF leads to reverse cardiac remodeling but only in patients with elevated CI. The variability of the response of systemic vascular resistance to AVF flow may explain this observation. Increased CI but not increased AVF flow may better determine candidates for AVF reduction.
Hypertension Research advance online publication, 26 May 2016; doi:10.1038/hr.2016.50

Keywords: aneurysmorrhaphy; arteriovenous fistula; arteriovenous fistula reduction; cardiac index; heart remodeling; high-flow

INTRODUCTION

A native arteriovenous fistula (AVF) is recommended for primary hemodialysis vascular access.[1] AVF is simultaneously like both a 'lifeline' and an 'Achilles heel,' because of volume overload of the heart.[2] AVF creation decreases systemic vascular resistance, thus leading to an increased cardiac index via increases in stroke volume, heart rate and left ventricular (LV) ejection fraction.[3] Extremely elevated AVF flow may lead to marked cardiac index elevation, volume overload-induced cardiac remodeling and clinical heart failure.[4,5]

To treat or prevent the development of heart failure, high-flow AVF are commonly closed or reduced. However, there are currently no clear indications to guide this practice. Increases in AVF flow are commonly considered when entertaining AVF modification. Basile *et al.*[6] have observed that vascular access flow ⩾2 l min^{-1} is associated with increased risk of high-output heart failure, and the Vascular Access Society defines high-flow AVF as AVF flow >1–1.5 l min^{-1}.[6] Nonetheless, the association of AVF flow and cardiac index is nonlinear, and there is high inter-individual variability in CI at the same level of AVF flow.[6,7] Until now, no study has evaluated whether the effect of high-flow AVF reduction on heart remodeling is modified by cardiac index (CI). Because cardiac remodeling is driven by increased venous return, which is equivalent to cardiac output, we hypothesized that an elevated cardiac index might better identify subjects with reverse remodeling after AVF reduction than increased AVF flow.

The aim of this study was to identify predictors of cardiac reverse remodeling after AVF reduction and to evaluate the effects of the baseline cardiac index on structural and functional changes in the heart.

METHODS

Population

All consecutive patients with high-flow (defined as AVF flow ⩾1.5 l min^{-1}) type I aneurysmatic AVF according to the Balaz classification scheme[8] referred to the Institute for Clinical and Experimental Medicine, Prague, Czech Republic for AVF reduction between January 2011 and October 2014 were included in this study. AVF flow and echocardiography were performed before the

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Received 21 January 2016; revised 16 March 2016; accepted 4 April 2016

operation and at 3 months and 1 year after the operation. The study complied with the Declaration of Helsinki. Informed consent was obtained from all patients. The study was approved by the local ethics committee.

AVF reduction

A reinforced aneurysmorrhaphy with external polytetrafluoroethylene mesh tube was used to reduce the high-flow AVF. This technique was developed by our group in 2008[9] and has been validated[10] and internationally adopted for aneurysmal AVF salvage.[11] A detailed video of this procedure can be found online (http://aneurysmorrhaphy.eu—How to use section). In brief, the aneurysmal fistula was mobilized, and general heparinization (5000–10 000 IU) was performed. The supplying artery and non-dilated vein above the aneurysm were clamped, and the aneurysmal sac was resected to an appropriate diameter. The vein wall was sewn with a continuous running suture. The repaired vein was scaffolded with an external mesh polytetrafluoroethylene prosthesis (ProVena; BBraun Medical, Melsungen, Germany), and arteriovenous re-anastomosis was performed. The distal anastomosis of an upper-arm AVF was relocated to forearm arteries, whereas a reduction of the distal anastomosis was performed in the case of a forearm AVF. Heparin was neutralized by protamine sulfate, and the wound was closed with drainage. All patients used 100 mg of acetylsalicylic acid after the operation. The AVF after aneurysmorrhaphy was usually used for dialysis after 4 weeks.

AVF flow measurement

AVF flow was measured in the brachial artery using an Aplio500 ultrasound system (Toshiba, Tokyo, Japan) as previously described.[2] AVF flow was calculated by multiplying the brachial artery cross-sectional area by the time-averaged mean velocity. The examinations were conducted by one angiology specialist with expertise in ultrasound examination.

Echocardiographic examination and hemodynamics

Echocardiographic examination was performed 24–48 h after dialysis to obtain similar and representative body fluid status. The examination was conducted by one medical doctor (VP) with expertise in echocardiography, and a Vivid7 ultrasound system (General Electric Healthcare, Wauwatosa, WI, USA) was used. The velocity–time integral in the LV outflow tract and the LV outflow tract diameter were used to calculate stroke volume and cardiac output. The cardiac index was calculated by dividing the cardiac output by the body surface area. A cardiac index $\geqslant 3.9\,l\,min^{-1}m^{-2}$ was considered the cutoff for an elevated cardiac index.[12] The LV mass was calculated by using the cube formula, as previously recommended.[13] The right ventricular systolic pressure was estimated from the tricuspid regurgitation velocity (available in 58% of patients), and the right atrial pressure estimate was based on the inferior vena cava diameter and collapsibility. The LV ejection fraction was used as a parameter of LV function, and the tricuspid annular plane systolic excursion was used as a parameter of right ventricular systolic function. The mean blood pressure (MBP) was calculated by using the equation MBP = 1/3 × SBP+2/3 × DBP, where SBP is the systolic blood pressure and DBP is the diastolic blood pressure. The total vascular resistance (TVR) was calculated as TVR = 80 (MBP/CO). The systemic vascular resistance (SVR, vascular resistance omitting AVF) was calculated as SVR = 80 (MBP/(CO-AVF flow)).

Statistical analysis

Continuous data with normal distributions are presented as the mean ± s.d. and non-normally distributed variables are presented as the median (interquartile range—IQR). Categorical data are shown as frequencies and percentages. To account for the correlation of measures on the same patient, a random-effect mixed-linear model[14] was used to assess the ability of baseline CI and AVF flow to predict LV diameter change after aneurysmorrhaphy. To increase the statistical power, and because we were interested in comparing the changes after operation between groups rather than determining the time point when these changes occurred, data examined at 3 months and 1 year after the operation were analyzed as a single time point (the after-operation time point). Patients were dichotomized on the basis of baseline CI ($<3.9\,l\,min^{-1}m^{-2}$—normal CI group, $\geqslant 3.9\,l\,min-1\,m^{-2}$—high CI group) and median AVF flow (<3.2 , $\geqslant 3.2\,l\,min^{-1}$). The null hypothesis tested was that the change in end-diastolic diameter after operation is independent of the baseline CI or AVF group. Differences between normal and high CI groups at baseline were compared using the *t*-test, Mann–Whitney *U*-test, χ^2 or Fisher exact test, as appropriate. The random-effect mixed-linear model was also used to analyze sequential data by the baseline cardiac index group. Gamma regression was used for right-skewed data. Calculations were performed with SPSS version 21 (IBM SPSS Statistics; IBM Corporation, Armonk, New York, NY, USA) and JMP10 (SAS Institute, Cary, NC, USA). A two-sided *P* value <0.05 was considered to be statistically significant.

RESULTS

In total, 32 patients with high-flow AVF without clinical signs of heart failure underwent AVF reduction between January 2011 and October 2014 in our institution. Two patients were excluded from analyses, owing to valvular heart surgery during the follow-up (one aortic valve replacement, one mitral valve replacement). Data from thirty patients (mean age 52 ± 12 years, 73% male) with high-flow AVF and a mean AVF flow of $3.3 \pm 1.1\,l\,min^{-1}$ (range $1.5–5\,l\,min^{-1}$) were analyzed. None of the patients included in the analyses had a significant valvular disease. As assessed by the corrected Akaike information criterion weight, linear regression (Figure 1) provided a better fit of the association between AVF flow and cardiac index (Akaike information criterion weight = 0.65, $R^2 = 0.13$) than did quadratic regression (Akaike information criterion weight = 0.35, $R^2 = 0.17$). At baseline, the LV end-diastolic diameter was associated with cardiac output (Pearson $r = 0.45$, $P = 0.03$) but not with AVF flow (Pearson $r = 0.13$, $P = 0.51$).

Predictors of reverse remodeling

The cardiac index discriminated patients with end-diastolic diameter (EDD) decrease after operation (interaction between CI group and time $P<0.01$), and increased CI was associated with EDD decrease after aneurysmorrhaphy ($P = 0.01$) (Figure 2a). However, AVF flow was not able to discriminate patients with EDD decrease after operation (interaction between AVF flow and time $P = 0.94$), and AVF flow over the median ($3.2\,l\,min^{-1}$) was not associated with an EDD decrease ($P = 0.07$) (Figure 2b). When EDD was adjusted for

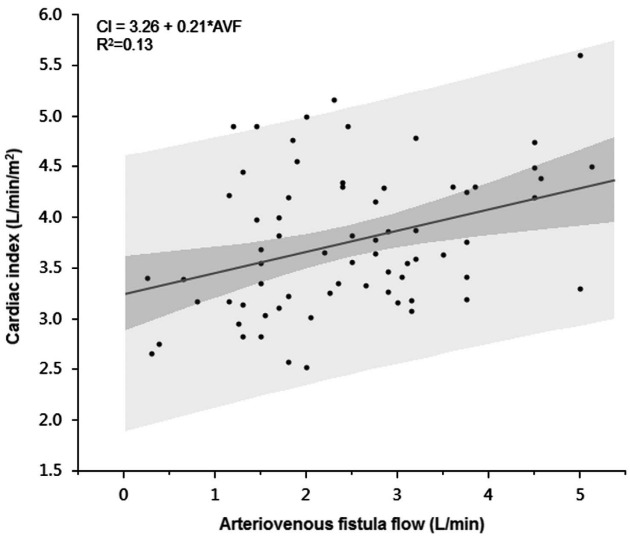

Figure 1 Association between arteriovenous fistula flow and cardiac index. Dark shaded area represents 95% CI of fit; light shaded area represents 95% CI of prediction. Data before and after operation are shown together. A full colour version of this figure is available online at the *Hypertension Research* website.

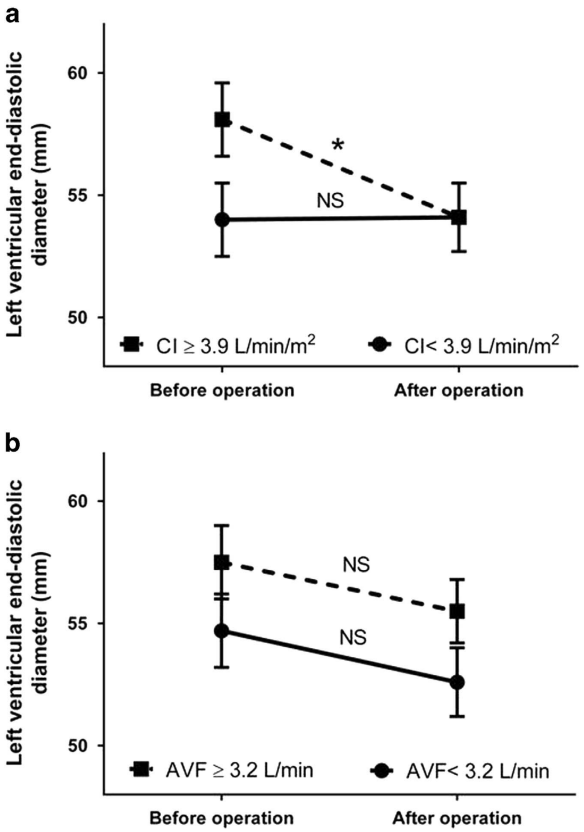

Figure 2 The influence of baseline cardiac index (**a**) and arteriovenous flow (**b**) on left ventricular end-diastolic diameter change after aneurysmorrhaphy. CI, cardiac index; AVF, arteriovenous fistula flow; $*P<0.05$ from baseline; NS, not significant. Estimated marginal mean +s.e.m. are shown.

body size (height or body surface area), the results did not change. Age ($P=0.78$), sex ($P=0.49$), baseline hemoglobin ($P=0.11$) and systolic blood pressure ($P=0.57$) did not predict EDD decrease after operation. On the basis of a univariate search for predictors of reverse remodeling, CI was the only predictor of LV diameter decrease after aneurysmorrhaphy. Thus, changes in other parameters of cardiac structure and function were analyzed by baseline CI category.

High CI and normal CI groups

There were 16 patients (54%) in the normal CI group (nCI) with $CI<3.9\,l\,min^{-1}m^{-2}$ (range 2.5–3.8 $l\,min^{-1}m^{-2}$) and 14 patients in the high CI group (hCI) (46%) with an increased cardiac index (range 4.0–6.0 $l\,min^{-1}m^{-2}$). Whereas the mean AVF flow did not differ between groups (3.1 ± 1.4 *vs.* $3.4\pm0.8\,l\,min^{-1}$, $P=0.34$ for nCI *vs.* hCI groups), there were significant differences in cardiac index, systemic vascular resistance, hemoglobin level and LV diameter between groups (Table 1).

The effect of aneurysmorrhaphy

After aneurysmorrhaphy, the nCI and hCI groups had similar reductions in AVF flow (−1.22 (−1.81 to −0.64) *vs.* −1.55 (−2.18 to −0.92) $l\,min^{-1}$, $P=0.45$) (Figure 3a). In contrast, the cardiac index decreased significantly only in hCI (−1.01 (−1.43 to −0.58) $l\,min^{-1}m^{-2}$, $P<0.001$) and not in the nCI group (−0.01 (−0.40 to 0.38) $l\,min^{-1}m^{-2}$, $P=0.97$) (Figure 3b). The total vascular resistance did not change in the nCI and increased in the hCI group (Figure 3c), whereas the systemic vascular resistance decreased in the nCI group and did not change in the hCI group (Figure 3d).

In the hCI group, there were significant decreases in LV end-diastolic diameter, mass, left atrial and right ventricular diameters, and estimated pulmonary systolic blood pressure (Table 2). In contrast, none of these parameters changed in the nCI group. There was a small decrease in the LV ejection fraction in both groups, but no patients developed new systolic dysfunction (EF < 55%). There was a small decrease in the parameters of right ventricular systolic function (tricuspid annular plane systolic excursion, Sm) in the hCI group, but after correction for right ventricular diameter change, this difference was not significant.

DISCUSSION

In the present study in patients with high-flow arteriovenous fistulas, we demonstrated that the effect of AVF reduction on heart remodeling is dependent on cardiac index before operation but does not depend on increased AVF flow. AVF flow reduction decreased LV end-diastolic diameter and mass, left atrial and right ventricular diameter and pulmonary pressure in the high CI group but not in the normal CI group. The variability of the response of systemic vascular resistance to AVF flow reduction may explain these observations.

Although several previous studies[7,15,16] have assessed the effects of AVF closure on the heart, this study is the first to address the effect of AVF reduction on heart remodeling. The advantages of aneurysmorrhaphy compared with ligation are the preservation of vascular access and an excellent long-term patency with minimal periprocedural complications.[10] In previously published studies, AVF closure has been shown to decrease left ventricular diameter and mass.[7,15,16] However, results of the present study show that the effect of AVF reduction on heart remodeling is not present in all patients and is dependent on cardiac index before operation but does not depend on increased AVF flow. This conclusion is supported by a previous observation of patients after kidney transplant undergoing AVF closure,[16] in which the magnitude of LV mass reduction was independent of AVF flow but correlated with baseline LV diameter and mass. In our study, left ventricular diameter at baseline was associated with cardiac output but not AVF flow, thus suggesting that LV dilatation is driven by increased cardiac output but not high-flow AVF.

In previous studies, the association between AVF flow and cardiac index/output has been found to be nonlinear.[6,7] In the present study, the association was linear but with high CI variability at the same level of AVF flow. This finding may be explained by a variable degree of systemic vasoconstriction/vasodilatation as a response to AVF creation. At baseline, despite similar AVF flow, patients in the hCI group had lower total vascular resistance and a higher cardiac index. Aneurysmorrhaphy in patients in the nCI group caused a decrease in SVR as a response to the AVF resistance increase, and thus, total vascular resistance and cardiac output did not change. In the hCI group, systemic vascular resistance did not change after aneurysmorrhaphy. Instead, the increase in total vascular resistance in these patients was coupled to decreasing cardiac output. The importance of the systemic vascular response found in our study is in line with results from a study by Unger *et al.*,[17] in which the decrease in LV mass and diameter after AVF closure was predicted by the acute increase in total vascular resistance and MBP during pneumatic compression of AVF. In another study,[18] the post-AVF closure 24 h diastolic blood pressure change (which is related to SVR) has been found to be negatively associated with LV mass change. This finding suggests that LV remodeling after AVF closure is present

Table 1 Descriptive statistics by cardiac index at baseline

Variable	*Normal cardiac index* (n = *16)*	*High cardiac index* (n = *14)*	P
Age, years	50.9 ± 9.1	53.0 ± 13.5	0.63
Gender (female), *n* (%)	4 (25)	4 (29)	0.83
Height, cm	173.5 ± 7.1	173.7 ± 6.5	0.94
Weight, kg	78.3 ± 15.6	80.6 ± 20.6	0.73
Systolic BP, mm Hg	134.4 ± 21.6	151.3 ± 20.1	**0.04**
Diastolic BP, mm Hg	77.6 ± 8.2	84.4 ± 13.5	0.11
Mean BP, mm Hg	96.5 ± 10.0	106.7 ± 13.9	**0.03**
Heart rate, bpm	67.6 ± 9.2	76.5 ± 9.0	**0.01**
Hemoglobin, g l^{-1}	118.4 ± 20.7	103.9 ± 15.3	**0.04**
AVF flow, l min^{-1}	3.1 ± 1.4	3.4 ± 0.8	0.34
Cardiac output, l min^{-1}	6.7 ± 1.8	9.7 ± 1.4	**<0.001**
Cardiac index, l $min^{-1}m^{-2}$	3.4 ± 0.7	4.8 ± 0.5	**<0.001**
TVR, dyn s cm^{-5} m^2	1187 ± 323	902 ± 229	**0.04**
SVR, dyn s cm^{-5} m^2	2183 ± 584	1551 ± 785	**0.04**
LV end-diastolic diameter, mm	54.1 ± 5.8	58.4 ± 5.6	**0.049**
LV mass, g	215.2 ± 87.2	263.5 ± 62.6	0.09
LV mass index, g m^{-2}	109.6 ± 45.7	135.2 ± 25.3	0.07
Relative wall thickness	0.37 ± 0.04	0.36 ± 0.04	0.64
LV hypertrophy, *n* (%)	7 (47)	9 (64)	0.34
LV remodeling, *n* (%)			0.41
Concentric remodeling	1 (7)	0 (0)	
Excentric hypertrophy	6 (40)	9 (64)	
Concentric hypertrophy	1 (7)	0 (0)	
LV ejection fraction, %	60.8 ± 5.2	61.6 ± 6.0	0.69
E/Em	13.4 ± 3.4	10.9 ± 8.5	0.39
Left atrial diameter, mm	42.1 ± 7.4	44.0 ± 5.9	0.45
RV diameter, mm	36.4 ± 4.1	40.0 ± 5.4	0.09
TAPSE, mm	22.1 ± 5.6	27.3 ± 5.8	0.06
Tricuspid Sm, m s^{-1}	12.8 ± 3.1	15.7 ± 3.6	0.05
RV dysfunction, *n* (%)	2 (13)	1 (8)	0.67
Pulmonary systolic BP, mm Hg	41.8 ± 14.3	39.8 ± 19.4	0.81
Inferior vena cava diameter, mm	16.4 ± 7.0	17.8 ± 5.0	0.56
Medication			
ACEi/ARB, *n* (%)	5 (31)	7 (50)	0.46
Beta-blockers, *n* (%)	13 (81)	10 (71)	0.68
Calcium channel blockers, *n* (%)	8 (50)	10 (71)	0.28
Diuretics, *n* (%)	10 (63)	10 (71)	0.71
Others, *n* (%)	3 (19)	6 (43)	0.24
Comorbidities			
Hypertension, *n* (%)	12 (75)	14 (100)	0.10
Diabetes, *n* (%)	1 (6)	1 (7)	1.0
Stroke, *n* (%)	0 (0)	1 (7)	0.47
Coronary heart disease, *n* (%)	3 (19)	2 (14)	1.0
AVF type			0.85
Radiocephalic, *n* (%)	7 (44)	5 (36)	
Brachiocephalic, *n* (%)	8 (50)	8 (57)	
Other, *n* (%)	1 (6)	1 (7)	

Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AVF, arteriovenous fistula; BP, blood pressure; LV, left ventricular; RV, right ventricular; RV Sm, peak systolic tricuspid annular velocity; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TVR, total vascular resistance.
Bold *P*-values are significant at the $P<0.05$.

only if the increase in total vascular resistance by AVF closure/reduction is not offset by the decrease in SVR.

The inability to increase systemic vascular resistance as a response to high-flow AVF and to decrease systemic vascular resistance as a response to increased AVF resistance after AVF closure/reduction suggests a vasomotor dysfunction in patients in the hCI group. One of the mechanisms affecting vasomotor function is anemia, which decreases systemic vascular resistance[19] and may cause high-output heart failure.[20] In the present study, though hemoglobin levels increased in patients in the hCI group, the hemoglobin increase did not significantly increase systemic vascular resistance, and adjustment for hemoglobin did not attenuate the decrease in LV diameter in this

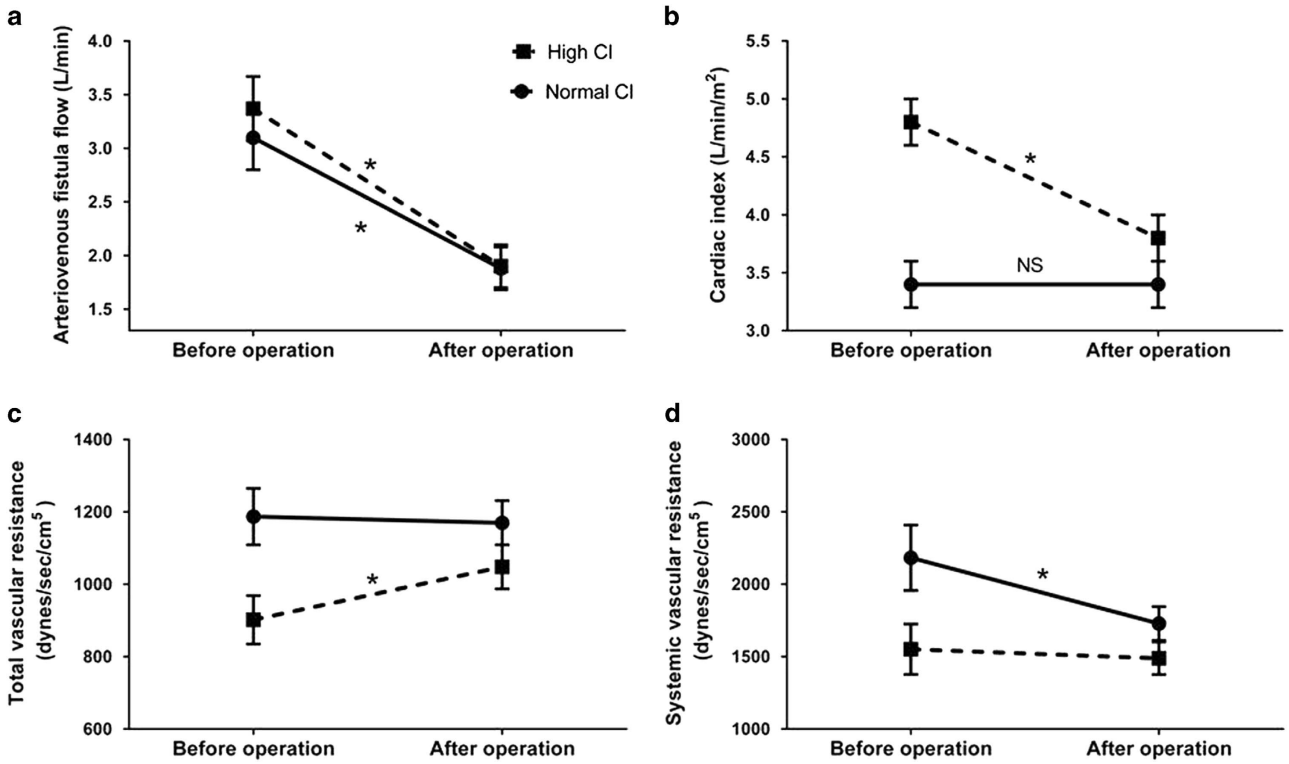

Figure 3 The effect of aneurysmorrhaphy on arteriovenous fistula flow (**a**), cardiac index (**b**), total vascular resistance (**c**) and systemic vascular resistance (**d**) by cardiac index (CI) on baseline. Significant changes from baseline ($P<0.05$) are marked by * Estimated marginal mean +s.e.m. are shown.

Table 2 Changes after aneurysmorrhaphy by baseline cardiac index

	Normal cardiac index		*High cardiac index*	
	Δ	P	Δ	P
AVF flow, l min^{-1}	−1.22 (−1.81 to −0.64)	**<0.001**	−1.55 (−2.18 to −0.92)	**<0.001**
CI, l $min^{-1}m^{-2}$	−0.01 (−0.40 to 0.38)	0.97	−1.01 (−1.43 to −0.58)	**<0.001**
TVR, dyn s cm^{-5} m^2	−17 (−168 to 134)	0.83	145 (8–282)	**0.04**
SVR, dyn s cm^{-5} m^2	−454 (−880 to −27)	**0.04**	−61 (−399 to 276)	0.72
Systolic BP, mm Hg	0.9 (−6.6 to 8.3)	0.82	−14.8 (−23.5 to −6.1)	**0.001**
Diastolic BP, mm Hg	−1.8 (−7.1 to 3.6)	0.51	−7.7 (−13.8 to −1.6)	**0.01**
Mean BP, mm Hg	−1.0 (−6.6 to 4.5)	0.71	−9.9 (−16.2 to −3.4)	**0.003**
Heart rate, bpm	−1.5 (−6.7 to 3.8)	0.58	−3.5 (−9.0 to 2.0)	0.21
Hemoglobin, g l^{-1}	−2.0 (−9.3 to 5.4)	0.60	10.8 (3.0 to 18.6)	**0.01**
LV end-diastolic diameter, mm	−0.5 (−2.5 to 1.4)	0.57	−4.5 (−6.6 to −2.3)	**<0.001**
LV mass index, g m^{-2}	−7.7 (−17.8 to 2.4)	0.13	−20.4 (−33.0 to −7.9)	**0.002**
Relative wall thickness	−0.01 (−0.03 to 0.02)	0.50	0.02 (−0.01 to 0.04)	0.28
LV ejection fraction, %	−2.5 (−4.7 to −0.3)	**0.03**	−2.9 (−5.2 to −0.5)	**0.02**
E/A	−0.14 (−0.37 to 0.10)	0.25	−0.26 (−0.50 to −0.02)	**0.04**
Left atrium diameter, mm	−0.3 (−1.8 to 1.3)	0.71	−2.5 (−4.1 to −0.8)	**0.004**
Right ventricle diameter, mm	1.5 (−0.9 to 3.9)	0.21	−4.5 (−7.4 to −1.5)	**0.004**
TAPSE, mm	0.5 (−2.5 to 3.4)	0.76	−5.1 (−8.6 to −1.6)	**0.005**
TAPSEc, mm	1.3 (−2.0 to 4.5)	0.44	−3.5 (−7.3 to 0.2)	0.07
RV Sm, m s^{-1}	0.5 (−1.0 to 1.9)	0.53	−2.5 (−4.5 to −0.6)	**0.01**
RV Smc, m s^{-1}	0.2 (−1.1. to 1.5)	0.80	−0.5 (−2.1 to 1.2)	0.58
RV/LV diameter ratio	0.03 (−0.02 to 0.08)	0.22	−0.03 (−0.08 to 0.03)	0.34
Inferior vena cava diameter, mm	−3.3 (−6.5 to −0.1)	0.04	−3.0 (−6.7 to 0.6)	0.10
Pulmonary systolic BP, mm Hg	0.05 (−8.1 to 8.2)	0.99	−7.7 (−14.9 to −0.5)	**0.038**

Abbreviations: **Δ**, change from baseline; AVF, arteriovenous fistula; BP, blood pressure; CI, cardiac index; E/A, mitral inflow early (E) to late (A) filling velocities; LV, left ventricular; RV, right ventricular; RV Sm, peak systolic tricuspid annular velocity; RV Smc, RV Sm corrected for RV diameter; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TAPSEc, TAPSE corrected for RV diameter; TVR, total vascular resistance.
Bold *P*-values are significant at the $P<0.05$.

group (Supplementary Table S1). Another mechanism that may explain abnormal vascular reactivity is autonomic dysfunction, which is common in patients with end-stage renal disease.[21] However, autonomic dysfunction was not evaluated in this study. Furthermore, we did not find any significant differences in baseline antihypertensive medications, thus suggesting that vasodilatative therapy is not responsible for this phenomenon.

There is an ongoing debate regarding whether AVF is beneficial or harmful in patients with end-stage renal disease.[22] In a retrospective study of dialyzed patients, no increased risk of death associated with high levels of AVF flow has been observed.[23] Thus, in most patients, AVF reduction/closure is not required; but clearly, among patients who develop adverse remodeling or heart failure, intervention may be required. On the basis of previous case reports, it seems reasonable to intervene in subjects with high-output heart failure, in which symptoms usually disappear after operation.[24] However, in more advanced stages of heart failure, patients may not benefit from the procedure.[23,25] The current results indicate that among patients without symptoms of heart failure, subjects with elevated cardiac index and left ventricular eccentric hypertrophy might be most likely to respond favorably to AVF reduction. In contrast, patients with high-flow AVF, normal cardiac index, no LV dilation and without symptoms of heart failure may not require surgical AVF reduction but instead would need close follow-up. Other causes of high cardiac index such as anemia, liver disease and hypervolemia should be excluded before intervention. Furthermore, other risk factors increasing morbidity and mortality in this population should be addressed.[26,27]

Our study should be interpreted within the context of its strengths and limitations. Though the sample size of the present study is relatively low, it is the first study to assess the influence of AVF reduction on the heart. Non-invasive hemodynamic data inherently have greater variability than invasive measurements. Echocardiographic assessments were performed after a short interval, and chronic effects of AVF reduction were not assessed. Because we did not measure symptoms of heart failure and functional capacity during the study period, we are unable to compare the effect of AVF reduction on those parameters. We also did not measure cardiac biomarkers, which may provide deeper insight into cardiac changes.

In conclusion, this study shows that in patients with end-stage renal disease, high-flow arteriovenous fistula reduction causes reverse cardiac remodeling only in patients with elevated cardiac output and thus high venous return. This finding suggests that an increased cardiac index, but not increased arteriovenous flow, may be the optimal parameter to assess when considering aneurysmorrhaphy or other AVF reduction techniques in a patient with a high-flow arteriovenous fistula.

CONFLICT OF INTEREST

BP and RS are the owners of BalRok clamp registration in the Office for Harmonization in the Internal Market (OHIM) Trade Marks and Designs and Community Design, RCD application number: 002024539. The other authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)

Eur J Vasc Endovasc Surg (xxxx) xxx, xxx

SYSTEMATIC REVIEW

Repair of Aneurysmal Arteriovenous Fistulae: A Systematic Review and Meta-analysis

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WHAT THIS PAPER ADDS
The present study brings important additional information to current aneurysmal access guidelines.

Objectives: Aneurysms arising from arteriovenous fistulae are a common finding among dialysed patients and pose a risk of acute bleeding. The aim of this study was to perform a systematic review and meta-analysis evaluating the surgical options for the treatment of aneurysmal arteriovenous fistulae.
Methods: A systematic review and meta-analysis of articles published between January 1973 and March 2019 describing the surgical treatment of arteriovenous fistulae aneurysms.
Results: A total of 794 records were identified. After duplicate and low quality studies were removed, 72 full text articles were reviewed and from these 13 were included in the meta-analysis. The total number of patients was 597. Aneurysms were located in the upper arm in 289 (59%) cases and the smallest diameter of a treated aneurysm was 15 mm. The most frequent indication for treatment was bleeding prevention in 513 (86%) cases. Aneurysmorrhaphy was the surgical method of choice in all 13 studies. The pooled primary patency at 12 months was 82% (95% CI 69%–90%, 12 studies, $I^2 = 84\%$, $p < .01$). The 12 month primary patency rates were similar for aneurysmorrhaphy with external prosthetic reinforcement (85%, 95% CI 71%–93%, two studies, $I^2 = 0\%$, $p = .33$) and aneurysmorrhaphy performed using a stapler (74%, 95% CI 61%–83%, four studies, $I^2 = 0\%$, $p = .48$) and without a stapler (82%, 95% CI 60%–94%, six studies, $I^2 = 92\%$, $p < .01$).
Conclusions: Aneurysmorraphy of arteriovenous fistulae is a procedure with acceptable short and long term results, with a low complication and aneurysm recurrence rate.

Keywords: arteriovenous fistula, vascular access, haemodialysis, aneurysm, pseudoaneurysm
Article history: Received 26 December 2018, Accepted 15 July 2019, Available online XXX

INTRODUCTION

Aneurysm formation is a complication of vascular access arteriovenous fistula (AVF) characterised by an enlargement of all three layers of the vessel wall with a diameter of more than 18 mm[1,2] and has a prevalence of more than 40% in the dialysis population.[3] Two different classification systems exist for arteriovenous fistula aneurysms (AVFAs). Balaz and Bjorck's classification[1] is based on the presence of a stenosis or thrombosis identified by ultrasound or fistulography. They describe type 1 as being without stenosis, type 2 with significant stenosis (≥50%) in either the inflow artery (2A), or at the arterial anastomosis (2B) or along the cannulation zone (2C), or in the central vein (2D), type 3 with partial thrombosis (≥50% lumen), and type 4 with complete thrombosis. Valenti *et al.*'s classification[2] describes four subtypes of AVFA based on external appearance. Type 1 is a dilatation of the whole (1a) or the proximal aspect of the AVFA (1b), type 2 has a "camel hump" appearance with at least one discrete aneurysm, type 3 is a complex and heterogeneous AVFA, and type 4 is a pseudoaneurysm. The primary purpose for the classification of AVFA is to allow standardisation of terminology to permit accurate communication in the literature. However, so far neither classification has been used widely in the literature.[3]

According to current clinical guidelines, treatment is usually only indicated for symptomatic aneurysms.[4–6] Three main groups of indications were identified through a literature search in 2015 conducted by Balaz and Bjorck,[1] which has been updated for the present meta-analysis. Group A

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https://doi.org/10.1016/j.ejvs.2019.07.033

Please cite this article as: Baláž P et al., Repair of Aneurysmal Arteriovenous Fistulae: A Systematic Review and Meta-analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2019.07.033

indications are related to patient discomfort, group B are related to bleeding risk and group C are related to access flow. Group C is divided into high flow fistulae, which poses a risk of heart failure and steal syndrome, and low flow fistulae with feeding artery, juxta-anastomotic, or inter-aneurysmal stenosis. Aneurysmal fistulae presenting only with outflow vein stenosis, which are otherwise asymptomatic should be treated primarily by endovascular intervention to the outflow stenosis. Asymptomatic aneurysmal fistulae should be treated conservatively; surgical treatment should be advocated only in special situations.[4–6]

Several different treatment options for AVFA with various different results have been described in the literature.[1] Unfortunately a comparative prospective or retrospective study evaluating the various different treatment options for AVFA has not yet been published and so recommendations for clinical practice regarding the optimal treatment for aneurysm repair are still lacking.

The aim of the present systematic review and meta-analysis was to perform and describe the character of surgically treated aneurysms, and to compare the results of the different surgical techniques.

METHODS

A systematic review of literature was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[7]

Registration

The study was registered in the international prospective register of systematic reviews PROSPERO, with registration number CRD42016029692.

Search strategy

MEDLINE, SCOPUS, Clinical Trials registry and Cochrane Central Register of Controlled Trials were searched. The (MeSH) search terms: haemodialysis arteriovenous access AND aneurysm were used for the searching. All databases were searched for articles published between January 1973 and March 2019.

Inclusion criteria

All eligible studies focussing on open or endovascular treatment of AVFA were included. Studies reporting results on both autologous and prosthetic arteriovenous fistulae were reviewed, but only data regarding autologous arteriovenous fistulae were extracted and included in the study.

Exclusion criteria

Studies which met the following pre-defined criteria were excluded:

(i) Studies focussing on prosthetic arteriovenous graft aneurysms or pseudoaneurysms only.
(ii) Conference abstracts, editorials, commentaries and studies without abstracts.
(iii) Studies not written in the English language.
(iv) Case reports (studies on one patient only).
(v) Studies with follow up periods of less than six months.
(vi) Studies where the results were not clear and were the authors mixed results of several types of techniques together and reported only cumulative results.

Data extraction

The titles and abstracts of studies were retrieved using the search strategy described above. References of all studies that met the inclusion criteria where reviewed independently by two review authors (S.R. and J.B.) to identify additional studies potentially meeting the inclusion criteria. Any disagreements over the eligibility of particular studies were resolved through discussion with a third reviewer (P.B.). Data from the included studies were uploaded into an excel spreadsheet. Extracted information included study setting, study population, description of the aneurysm, indication for treatment, type of treatment, type of complications, and patency rate after intervention.

Definitions of extracted information

Study setting: randomised control trials (RCTs), case series, case control series, cross sectional studies, cohort studies, prospective studies, retrospective studies.

Demographic data: gender, age, time between arteriovenous fistula creation and aneurysm development.
Description of the aneurysm: diameter, shape, presence of stenosis or thrombosis, location
Indication for treatment: bleeding prevention, insufficient high or low flow, patient discomfort, cosmetic reasons.

Types of treatment

(i) Aneurysmorrhaphy (also referred to as aneurysmectomy or aneurysmoplasty): resection of the aneurysmal wall followed by primary closure either by hand sutures or a stapler with or without external reinforcement.
(ii) Plication: suturing the aneurysmal sac without resection.
(iii) Resection: resection of the AVFA followed by prosthetic or venous substitution.
(iv) Ligation and bypass: ligation of the aneurysm segment with bypass rerouting.
(v) Endovascular repair: Insertion of a covered stent graft endovascularly into the lumen of the AVFA.

Please cite this article as: Baláž P et al., Repair of Aneurysmal Arteriovenous Fistulae: A Systematic Review and Meta-analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2019.07.033

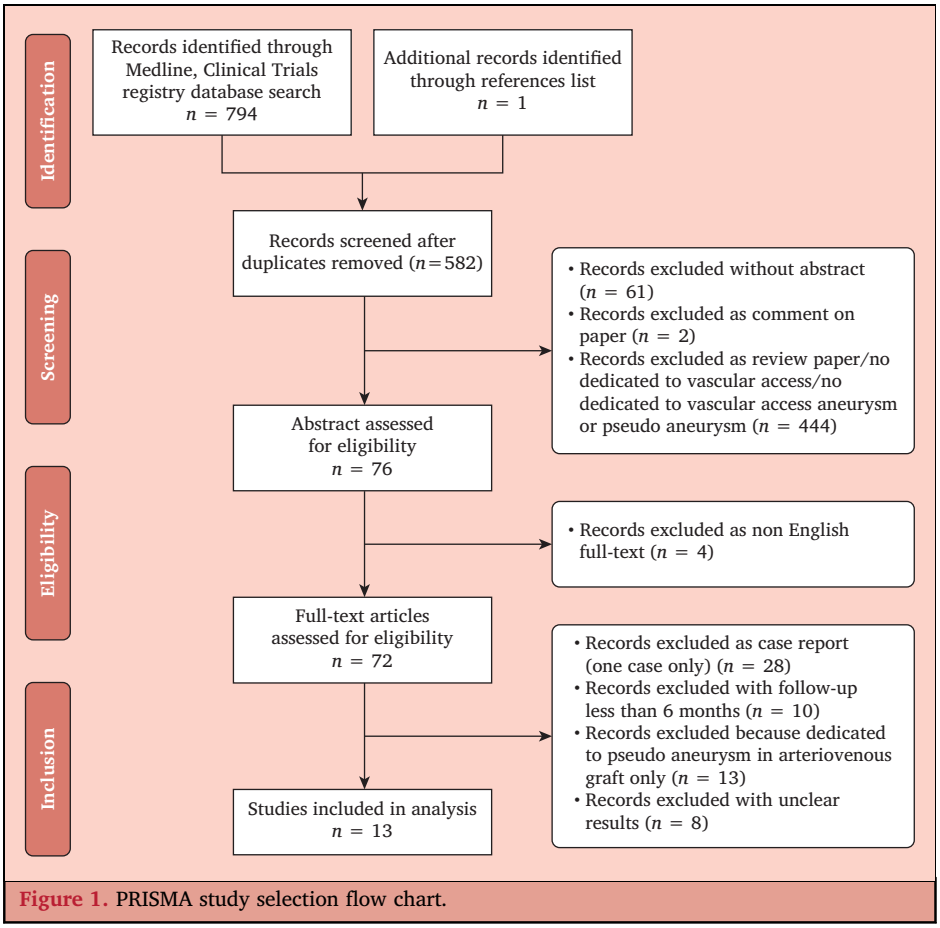

Figure 1. PRISMA study selection flow chart.

Complication and patency: post-operative complication and patency rates were defined in accordance with recommended standards.[8]

Quality assessment

The quality of the included studies was independently assessed by two reviewers (S.R. and J.B.) using the checklist for quality appraisal of case series studies produced by the Institute of Health Economics, Alberta, Canada.[9] This checklist consists of 20 items, of which 15 were considered applicable to the present study. Each study received one point for each item that was fulfilled on this checklist. The maximum and minimum numbers of points for each study were 15 and 0, respectively. Studies were classified as high quality if they received 13 or more points, moderate quality if they received 11–12 points and low quality if they received 10 points or less.

Statistical analysis

Pooled mean patient age and procedure and hospital length of stay were calculated by multiplying the mean by the sample size in each study and then dividing the sum of each of these values by the total sample size. Interval data for primary patency at 12 months was extracted as follows. The number of patients included in each study at 12 months was derived from survival curves or from the study results text. The absolute number of cases with primary patency was then calculated from the number of patients included in each study at 12 months and the percentage primary patency reported in the study at 12 months. Reported complication rates were extracted along with the number of patients included at the start of the study. A log transformation of raw patency rates and complication rates was performed before carrying out a meta-analysis using a random effects model with the DerSimonian and Laird method. Subgroups were identified on the basis of whether an aneurysmorrhaphy was reinforced with external prosthesis, performed with a stapler or not. Heterogeneity was assessed by estimating between studies variance (tau^2) and by calculating the proportion of total variability explained by between study variability (I^2). Heterogeneity was considered significant if $p < .10$ or I^2 exceeded 30%. Significance testing for publication bias and meta-regression to identify between study predictors of effect size was performed since overall more than 10 studies were included in the meta-analysis.[10] For meta-regression mixed effects models were constructed using restricted maximum likelihood and single modifiers. Statistical tests for meta-analysis were performed on R version 3.4.0 (R Foundation for Statistical Computing) using the meta package.[11]

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Table 1. Characteristics of the 13 case series describing management of aneurysmal arteriovenous fistulae included in the systematic review

Study Year	Patients – *n*	Definition of the aneurysm (smallest diameter)	Technique of repair	Follow-up	Cannulation	Primary patency at 1 year	Remarks
Pierce *et al.*[30] 2007	12	20 mm	Aneurysmorrhaphy with a stapler device and oversewing the staple line	29 months	After 48 hours in 5/12 pts, after one month in 7/12 pts	75%	• High flow reduction was performed in one patient • Recurence of aneurysm ($n = 2$)
Berard *et al.*[23] 2010	33	20 mm	Aneurysmorrhaphy with atraumatic steel cannula supported with external prothesis	12 months	after 1 month	93%	• High flow reduction was performed in 16 patients
Woo *et al.*[27] 2010	19	40 mm	Aneurysmorrhaphy with using red rubber catheter	23 months	After 1 month	92%	• Two central vein stenosis was confirmed and treated before surgery • Thrombosis ($n = 1$)
Hossny *et al.*[24] 2013	14	25 mm	Aneurysmorrhaphy with nelaton catheter	30 months	After 1 month	86%	
Rokosny *et al.*[20] 2014	62	40 mm	Aneurysmorrhaphy with BALROK clamp supported with external prothesis https://www.youtube.com/watch?v=59V1y9a6Z4c&t=42s	15 months	after 1 month	79%	• High flow reduction was performed in 24 patients • Bleeding ($n = 3$), Infection ($n = 1$), Stenosis ($n = 6$)
Tozzi *et al.*[21] 2014	14	15 mm	Aneurysmorrhaphy with articulating linear stapler with vascular cartridges and without oversewing the staple line	17 months	Immediately after surgery	86%	• Three central vein stenosis was confirmed and treated before surgery
Piccolo *et al.*[28] 2015	10	30 mm	Aneurysmorrhaphy with 2.5 mm TA stapler and without oversewing the staple line in nine of the ten patients	11 months	Immediately after surgery	80% at 6 months	• Thrombosis ($n = 1$)
Patel *et al.*[29] 2015	48	N/A	Aneurysmorrhaphy	12 months	Less than six weeks	73%	• 43 central vein stenosis was confirmed and treated before surgery • Stenosis required angioplasty ($n = 13$)
Vo *et al.*[25] 2015	40	30 mm	Aneurysmorrhaphy with 3.5 mm TA and Endo GIA staplers and oversewing the staple line	20 months	After 1 month	67% at 10 months	• 19 central vein stenosis was confirmed and treated before surgery • Recurence of aneurysm ($n = 2$)
Wang and Wang[22] 2017	185	N/A	Partial aneurysmorrhaphy	27.9 +/− 21.9 months	Immediately	45%	• 96% primary assisted patency at 1 year • 50 central vein stenosis was confirmed and treated before surgery • Thrombosis ($n = 1$), Bleeding ($n = 1$), Skin necrosis ($n = 1$), Skin nonhealing ($n = 4$)
Nezakatgoo *et al.*[31] 2018	102	N/A	Aneurysmorrhaphy with using thoracostomy tube with 90-degree rotation	36 months	After 24 hours	91% at 95 months	• Thrombosis ($n = 5$), Steal syndrome ($n = 7$), Stenosis ($n = 3$), Infection ($n = 2$) • Recurence of aneurysm ($n = 7$)

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Table 1-*continued*

Study Year	Patients — *n*	Definition of the aneurysm (smallest diameter)	Technique of repair	Follow-up	Cannulation	Primary patency at 1 year	Remarks
Moskowitz *et al.*[32] 2018	17	N/A	Aneurysmorrhaphy with stapler and oversewing the suture	12.5 months	Immediately	94%	• 14 central vein stenosis was confirmed and treated before surgery
Wan *et al.*[26] 2019	41	18 mm	Anuerysmorrhaphy using a 6mm catheter as a guide for aneurysm sac resection	27 months	58% immediately, 32% on 3rd day, 10% after two weeks	95%	• Flow reduction of 1618 to 772 mL/min ($p < .01$) after aneurysmorrhaphy was achieved • Stenosis ($n = 7$)

N/A = not applicable.

Ethics approval statement

No ethics approval or patient consent were required for this type of study.

RESULTS

Search results and study characteristics

In total 794 records were identified using the search strategy. None of these studies were RCTs, case control studies, cross sectional studies or cohort studies. After reviewing these records, 582 duplicates, 61 records without abstracts and two commentaries were removed. A further 444 records were removed because they were either review papers or were not dedicated to aneurysms or pseudoaneurysms of AVF or prosthetic arteriovenous grafts. After assessing the abstracts of the remaining 76 records, four were removed because they were not written in the English language. Seventy-two full text papers were assessed for eligibility. Twenty-eight were removed as they were case reports (each describing only one patient), 10 were excluded because the follow up was less than six months, and 13 were excluded as they were performed only on patients with pseudoaneurysms of arteriovenous grafts and not fistulae. Six studies were removed because it was not possible to extract data pertaining only to true aneurysms of autogenous AVFAs. Two studies were removed as they lacked data on demography, complications, patency and follow up.[12–19] In total, thirteen case series met the inclusion criteria and were included in the meta-analysis (Fig. 1, Table 1).

Study quality assessment

None of the included studies were RCTs or prospective case series with control groups. All were descriptive retrospective case series. Based on the results obtained from the "Quality Appraisal Checklist for Case Series Studies" no studies reached the maximum score. The papers by Rokosny *et al.*,[20] Tozzi *et al.*,[21] and Wang and Wang[22] attained 13 points and were assigned as high quality studies according to the methodology. A rating of moderate quality (11—12 points) was attained by four studies,[23–26] and six studies were rated as low quality (10 points and less).[27–32] The quality assessment is summarised in Table 2.

Patient characteristics

The overall number of patients from all thirteen studies was 597. Mean patient age was reported in nine of the included studies; the pooled mean age was 55.5 years. There were more male than female patients, with the proportion of male patients ranging between 53% and 79%. Indications for treatment according to Balaz and Bjorck[1] were described in all but one study.[28] Twenty-one patients (4%) were assigned to group A, 513 (86%) to group B and 53 (10%) to group C.

Description of the aneurysms

The location of the aneurysm was reported in all but one study.[31] The most frequent location was the upper arm (brachiocephalic and brachiobasilic fistulae) in 289 (59%) patients, followed by 205 (41%) forearm AVFAs. Only one case occurred in the lower extremity. The diameter of the treated aneurysms ranged from 15 to 80 mm. Time from creation of AVF to the treatment of the aneurysm was described in the most of studies with the shortest time being 12 months and the longest 144 months. Other parameters, such as the presence of stenosis or occlusion and the external appearance of the aneurysms were not systematically described according to the proposed classification systems.[1,2]

Type of treatment

The aneurysms were treated by aneurysmorrhaphy in all 13 studies. The aneurysmorrhaphies were performed with different types of devices and instruments inserted into the aneurysmal vein to facilitate resection after disconnection from the feeding artery (see Table 1). In five studies aneurysmorrhaphy was performed using a

Table 2. Summary of quality assessment of the 13 case series describing management of aneurysmal arteriovenous fistulae included in the systematic review

Study	Quality assessment question															Total points
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	
Pierce *et al.*[30] / 2007	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	8
Berard *et al.*[23] / 2010	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Woo *et al.*[27] / 2010	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	8
Hossny *et al.*[24] / 2013	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Rokosny *et al.*[20] / 2014	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Tozzi *et al.*[21] / 2014	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Piccolo *et al.*[28] / 2015	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes	Yes	5
Patel *et al.*[29] / 2015	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9
Vo *et al.* [25] / 2015	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Wang and Wang [22] / 2017	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Nezakatgoo *et al.*[31] / 2018	Yes	No	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Moskowitz *et al.*[32] / 2018	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	8
Wan *et al.*[26] / 2019	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12

Yes: 1 point; No: 0 Points.
A- Was the hypothesis/aim/objective of the study clearly stated?
B- Was the study conducted prospectively?
C- Were the cases collected in more than one centre?
D- Were patients recruited consecutively?
E- Were the characteristics of the patients included in the study described?
F- Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?
G- Was the intervention of interest clearly described?
H- Were additional interventions (co-interventions) clearly described?
I- Were relevant outcome measures established a priori?
J- Were the relevant outcomes measured using appropriate objective/subjective methods?
K- Were the statistical tests used to assess the relevant outcomes appropriate?
L- Was follow-up long enough for important events and outcomes to occur?
M- Were losses to follow-up reported?
N- Were the adverse events reported?
O- Were the conclusions of the study supported by the results?

stapler.[21,25,28,30,32] In two studies the repaired AVFs were reinforced with external mesh prosthesis.[20,23] Dialysis was performed through a central catheter or through the repaired AVFAs immediately after surgery depending on the technique. In the majority of studies when cannulation was performed immediately after surgery, the non-repaired part of AVFAs was used for cannulation (Table 1). The mean procedure time was reported in six studies and ranged from 130 to 188 min with pooled mean of 146 min.

Central vein stenosis

Stenosis of the outflow central vein was reported in six studies[21,22,25,27,29,32] and was confirmed in 131 (21%) patients. All these patients were treated endovascularly. Routine fistulography for the evaluation of central vein stenosis was performed in two studies.[27,29]

Post-operative outcome

Primary patency. In the study by Vo *et al.*[25] follow up was at least 10 months for 75% of the patients so the total number of patients included at 10 months was also used as the 12 month figure. In the study by Tozzi *et al.*[21] no patient was lost during follow up with a median follow up was 16.5 months (IQR, 14–20.5 months) so the number of patients included at the outset of the study was used for the total number of patients at 12 months. In the study by Nezakatgoo *et al.*[31] the follow up period was between seven months and 95 months and a decision was taken to include all patients from this study even though a small percentage may not have been followed up for a full 12 months. In the study by Piccolo *et al.*[28] patency was only reported at six months so this study was excluded from the patency analysis. In all the other studies 12 month primary patency was reported or could be calculated. The pooled primary patency rate at 12 months was 82% (95% CI 69%–90%, 12 studies $I^2 = 84\%$, $p < .01$). There were similar 12 month primary patency rates between aneurysmorrhaphy with external prosthetic reinforcement (85%, 95% CI 71%–93%, two studies, $I^2 = 0\%$, $p = .33$) and aneurysmorrhaphy performed using a stapler (74%, 95% CI 61%–83%, four studies, $I^2 = 0\%$, $p = .48$), and without using a stapler (82%, 95% CI 71%–93%, six studies, $I^2 = 92\%$, $p < .01$) (Fig. 2). Meta-regression was undertaken to identify between study predictors of effect size. Mixed effects models were constructed using restricted maximum likelihood and the following single modifiers; technique (external prosthesis, stapler and others), year of publication, study quality and sample size. Only sample size was a significant moderator ($R^2 = 31\%$, $p = .05$) but did not account completely for the

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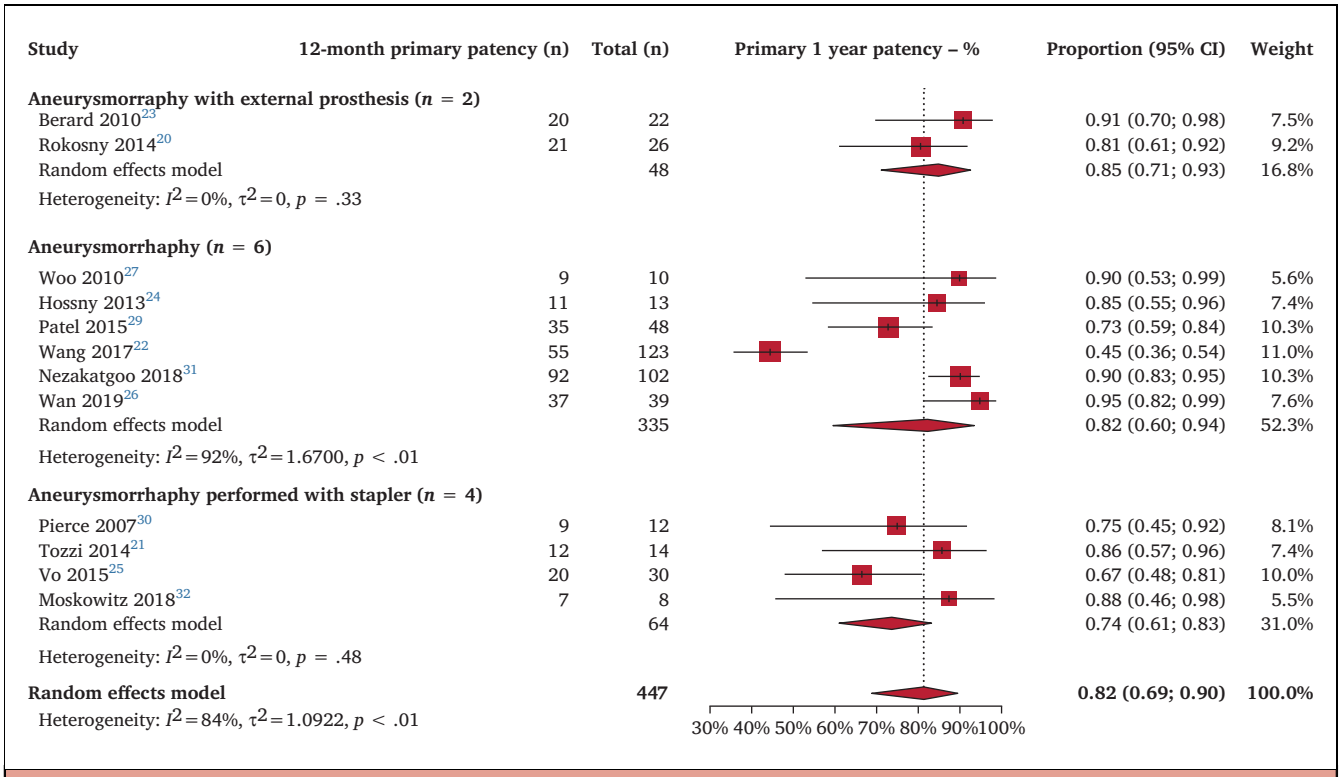

Figure 2. Forest plot for primary patency after aneurysmorrhaphy. CI = confidence interval.

overall heterogeneity encountered in the meta-analysis. Potential publication bias in terms of an absence of smaller studies reporting lower patency rates was evident on inspection of the funnel plot (Fig. 3) and on statistical testing (Egger test, $p = .007$).

Post-operative complication related to aneurysmorrhaphy. Post-operative complications were reported in eight studies.[20,22,23,26–29,31] Overall 20 (3%) cases developed early post-operative complications in the first 30 days after surgery. The most frequent complication was a haematoma, which occurred in 14 cases (2%). Two patients developed acute thrombosis (0.3%) and one patient after aneurysmorrhaphy reinforced with an external prosthesis ($n = 95$) developed infection of the graft (1%). Late post-operative complications (more than 30 days) occurred in 42 cases (7%) and were reported in six studies.[20,23,26,27,29,31] There were three late infections of the exoprosthesis (3%), seven late thromboses (1%) and one case of skin necrosis. The pooled complication rate was 11% (95% CI 7%–18%, 13 studies $I^2 = 67\%$, $p < .01$). Complication rates were similar between aneurysmorrhaphy with external prosthetic reinforcement (7%, 95% CI 1%–46%, two studies, $I^2 = 67\%$, $p = .08$) and aneurysmorrhaphy performed using a stapler (4%, 95% CI 1%–12%, five studies, $I^2 = 0\%$, $p = .79$) and without a stapler (15%, 95% CI 8%–27%, six studies, $I^2 = 81\%$, $p < .01$) (Fig. 4). Meta-regression was undertaken to identify between study predictors of effect size. Mixed effects models were constructed using restricted maximum likelihood and the following single modifiers; technique (external prosthesis, stapler and others), year of publication, study quality and sample size. No significant moderators were identified. An absence of smaller studies reporting higher complication rates was evident on inspection of the funnel plot (Fig. 5) although no significant publication bias was identified on statistical testing (Egger test, $p = .057$).

Length of hospital stay. Mean hospital stay was reported in seven studies. Pooling these averages resulted in a total mean hospital stay of 1.8 days. In the study by Moskowitz *et al.*[32] aneurysmorrhaphy was performed in an outpatient setting.

Aneurysm recurrence. Information about new aneurysm development has been reported in all but one study.[22] In 12 included studies development of new aneurysms after aneurysmorrhaphy in the defined follow up was observed in 11 of 434 patients (3.0%) and occurred in three studies.[25,30,31]

DISCUSSION

Symptomatic vascular access aneurysms may present with pain, risk of bleeding due to skin erosion or necrosis, skin infection and prolonged bleeding after haemodialysis, which in some cases may be fatal. Current guidelines, including the most recent one from the European Society for Vascular and Endovascular Surgery (ESVS) published in 2018, recommend surgical intervention for symptomatic aneurysms, but do not give any strict recommendations on the appropriate type of intervention.[4–6] The present

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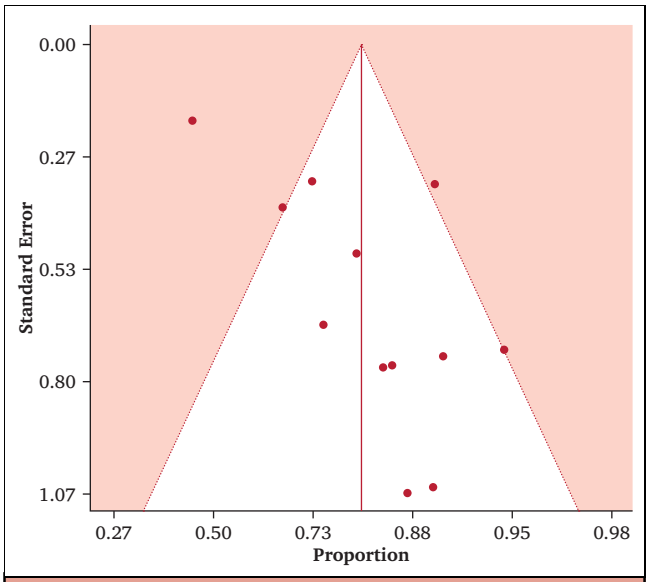

Figure 3. Funnel plot for visual inspection of the potential for publication bias for the outcome 12 month primary patency. The plot shows a potential absence of smaller studies reporting lower patency rates.

systematic review and meta-analysis fills this important scientific gap in the current guidelines and further explores the guideline statement that very little literature exists on the surgical treatment of the vascular access aneurysm.[4] The first published case on the surgical treatment of a vascular access aneurysm was written in 1973 by Hashmonai *et al*.,[33] who performed resection and ligation of a vascular access aneurysm. Since then the surgical treatment of vascular access aneurysms has developed greatly. At present, there are five types of surgical technique for the treatment of vascular access aneurysms. These are aneurysmorrhaphy (also known as aneurysmectomy or aneurysmoplasty), plication, resection with substitution, ligation, and endovascular repair. In the present review strict inclusion criteria were used so that all papers focusing on the surgical treatment of native and prosthetic AVFAs could be found. Papers focused solely on prosthetic access were excluded, together with non-English papers and case reports as well as studies with follow up less than six months. The systematic review identified a limited evidence base with only case series and no comparative studies.

The first important observation was that the majority 563 (94%) of the treated aneurysms were symptomatic. This finding is in accordance with the current guidelines, which recommend that treatment should be offered mainly for symptomatic aneurysms and that asymptomatic aneurysms with cosmetic concerns should be assessed very carefully in an individual setting. The most frequent indication for surgical treatment (86%) was bleeding prevention, which was indicated for group B aneurysms of the Balaz and Björck classification.[1]

Balaz and Björck[1] and Valenti *et al*.[2] suggest defining an AVA aneurysm as a dilation with a minimal diameter of 18 mm. It was noted that similar cut off values had been used to define aneurysms in the included articles, except the study by Tozzi *et al*.,[21] in which the minimum diameter was 15 mm. The most frequent location of the aneurysm was the upper arm (59%).

The rest of the meta-analysis focused on the evaluation of aneurysmorrhaphy, which was the technique of the choice in all 13 studies included in the meta-analysis. All but one study[28] reported primary patency at least 12 months after aneurysmorrhaphy and were included in patency analysis. The pooled primary patency rate at 12 months was 82%. However, a potential for publication bias was identified in the reporting of primary patency rates and it may be that in clinical practice lower rates of primary patency are observed. Twelve of the included studies for primary patency evaluation reported primary patency between 67% and 100%, except for the study by Wang and Wang,[22] which reported a primary patency at one year of 45%. However, primary assisted patency dramatically increased in the aforementioned study[22] after endovascular patency maintaining procedures (96% at one year). The explanation for the low primary patency in this study is probably related to the strict criteria of fistulography followed by endovascular procedure for stenoses greater than 50%.[22]

Reinforced aneurysmorrhaphy was used in two studies.[23,20] The rationale to improve patency by reinforcing the vein after aneurysmorrhaphy with an external prosthesis was introduced by Balaz *et al*. in 2008.[34] This idea was adopted from peripheral venous bypass surgery where varicose saphenous veins can be stabilised externally with prostheses to allow them to be used as conduits.[35] Neither of the two studies that used external prostheses proved that this led to better patency; the 12 month primary patency rates were similar. Unfortunately, infective complications were noted in four cases in studies that used an external prosthesis.[20,23] Although it was not confirmed that an external prosthesis leads to improved patency, the team is currently conducting a prospective randomised control trial to compare aneurysmorrhaphy with and without external support (AVAH trial, clinicaltrials.gov identifier: NCT03262467).

A surprising finding was that in the studies included in the meta-analysis none described covered stent graft implantation. Similar to aortic aneurysms the authors thought that stent grafts would be used widely in the treatment of vascular access aneurysms. The main problem with stent graft implantation is probably the need for suitable landing zones for implantation. Furthermore, cannulating stented aneurysms is problematic and stent grafts are associated with additional complications such as a high incidence of infection, stent fracture, development of pseudoaneurysms and stent graft disintegration.

A frequently discussed issue is the need for temporary central venous catheter insertion to allow the repaired aneurysm time to heal before it is used. Central catheters were used for haemodialysis for four weeks after surgery in seven studies;[20,23–25,27,29,30] in the rest of the studies dialysis was performed through the repaired fistula in the immediate post-operative period. Dialysis performed in the immediate

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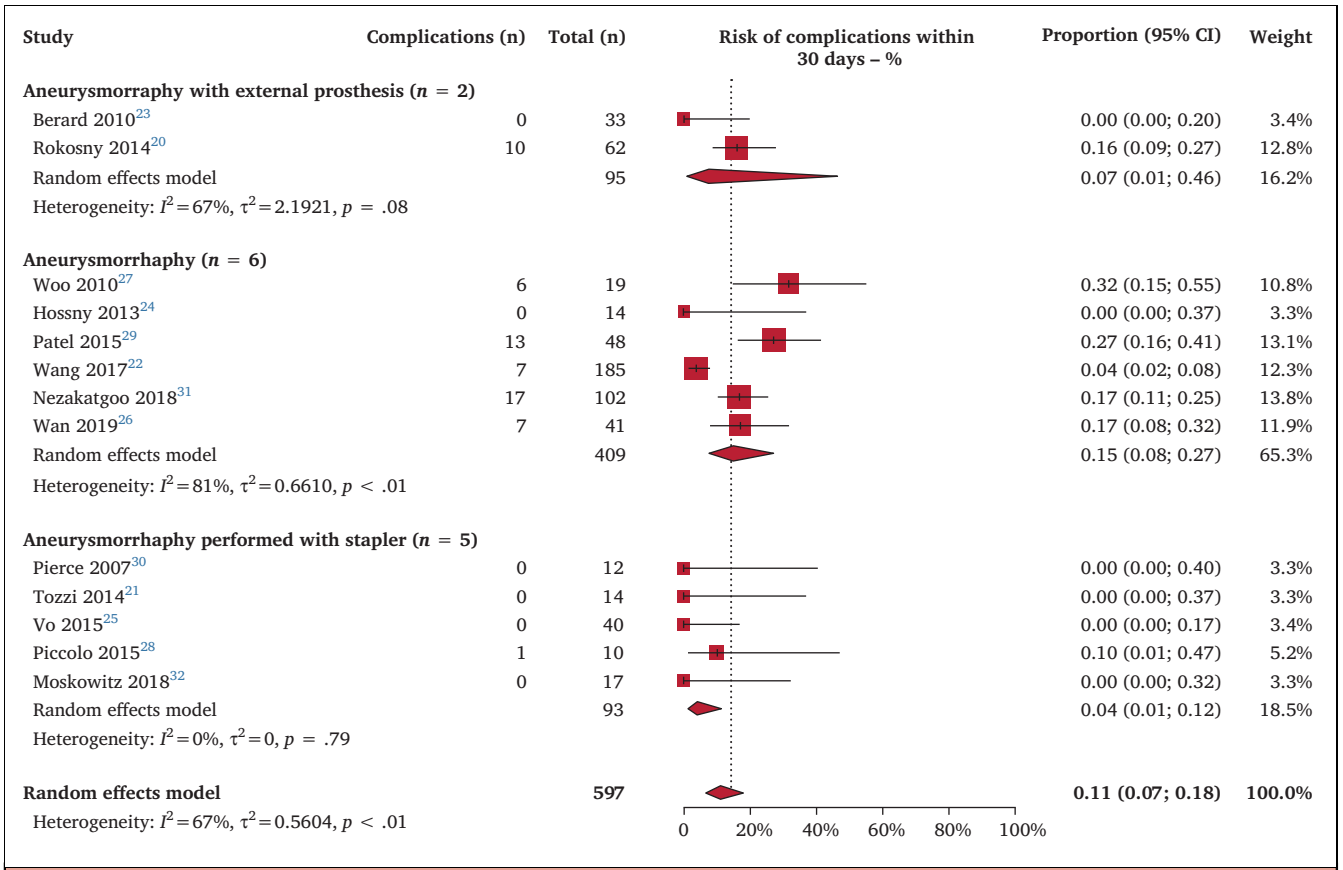

Figure 4. Forest plot for complications after aneurysmorrhaphy. The complications used in this analysis were the total complications reported in each study as listed in Table 1.

post-operative period through the repaired fistula was done either in fistulae repaired by staplers or in the proximal part of the fistula where the surgery had not been performed. In the study by Nezakatgoo *et al.*[31] immediate cannulation was performed after aneurysmorrhaphy with 90° rotation of the vein in a new tunnel for the repaired AVFA (Table 1). Most of the authors of the staple aneurysmorrhaphy papers believed that the risk of bleeding from a vein sutured by hand is higher than from a vein repaired with a stapler. The question whether stapled aneurysmorrhaphy is safer for immediate cannulation remains unanswered and should be addressed by a prospective comparative study in the future. Another important issue is the extent of dissection of the venous arm. In situations when the surgeon was able to leave part of the vein without aneurysmorrhaphy it could be used for immediate cannulation after surgery thus avoiding the risk of bleeding from sutured veins. Unfortunately, this issue was not systematically described in the included studies. Finally, in terms of aneurysm recurrence, aneurysmorrhaphy seems to be a safe technique with less than 3% of recurrence in one year.

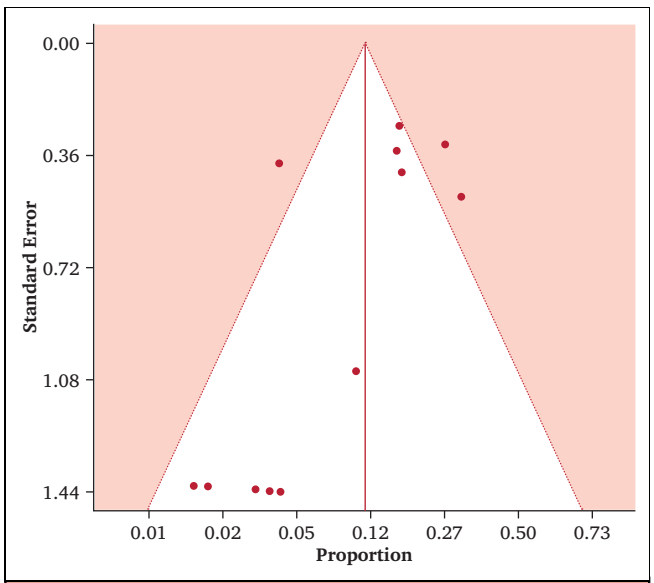

Figure 5. Funnel plot for visual inspection of the potential for publication bias for the outcome complications. The plot shows a potential absence of smaller studies reporting higher complication rates.

Logically, central vein stenosis seems to be the biggest factor for AVFA development. Outflow vein stenosis was found in 21% of the patients and these findings were strongly dependent on whether routine pre-operative fistulography was performed. From this point of view, it is suggested that routine fistulography is not mandatory and should be performed only when ultrasound signs of outflow vein stenosis are suspected.

Based on the present systematic review and meta-analysis, the authors believe that all symptomatic

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aneurysmal arteriovenous access fistulae should be treated surgically by aneurysmorrhaphy without external reinforcement. Aneurysmorrhaphy as a salvage technique using the remaining healthy venous wall of the repaired access is a safe procedure with long term patency, low complication and recurrence rates. For this purpose, aneurysmorrhaphy performed with or without a stapler device seems to be the preferred option. When central vein stenosis is confirmed, an endovascular approach to the underlying stenosis is recommended. Finally, asymptomatic aneurysmal fistulae are preferably treated conservatively.

CONFLICT OF INTEREST

None.

FUNDING

None.

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Review article – *Special issue: Panvascular medicine*

Contemporary management of arteriovenous haemodialysis fistula aneurysms

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ARTICLE INFO

Article history:
Received 18 July 2017
Received in revised form
10 October 2017
Accepted 10 October 2017
Available online 8 November 2017

Keywords:
Aneurysm
Arteriovenous fistula
Arteriovenous access
Haemodialysis
Treatment

ABSTRACT

Introduction: Aneurysms develop in up to 60% of patients with an arteriovenous fistula. Frequently arteriovenous fistula aneurysms are asymptomatic with the presence of symptoms potentially heralding the development a significant complication. A range of surgical and endovascular techniques are available to manage arteriovenous fistula aneurysms but clinical guidelines regarding the appropriate application of each approach are lacking. This review will examine the presentation, indications for treatment and management options for arteriovenous fistula aneurysms.

Methods: A non-systematic review of published literature in the following databases was performed: Medline, ScienceDirect, Scopus and the Cochrane Database of Systematic Reviews. Publications relating to arteriovenous fistula aneurysms and treatment options between January 1973 and June 2016 were considered for inclusion. Articles pertaining to aneurysms and pseudoaneurysms of prosthetic arteriovenous access sites were excluded. The literature search was supplemented by a review of the author's experience.

Results: Arteriovenous fistula aneurysms are defined by an expansion of the intimal, medial and adventitial layers of the vessel wall to a diameter of more than 18 mm. Treatment of arteriovenous fistula aneurysm is indicated if there is pain, risk of haemorrhage and flow disturbance (either low or high flow). When deciding on whether to actively treat or observe, the diameter of the arteriovenous fistula aneurysm and cosmetic concerns should not be considered in isolation. Commonly applied approaches for treating arteriovenous fistula aneurysm are resection with interposition, remodelling and insertion of an endovascular stent graft. Although various surgical and endovascular options have been reported, there are no prospective studies directly comparing techniques.

Conclusions: Asymptomatic aneurysms can be safely observed. Due to a lack of sufficient evidence base, no individual management strategy can currently be recommended for aneurysms requiring treatment. Finally, symptomatic aneurysms, mainly which are in the high risk of bleeding, should be indicated for the treatment as soon as possible.

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https://doi.org/10.1016/j.crvasa.2017.10.005

Contents

Introduction

Renal replacement therapy for patients with end stage renal failure comprises haemodialysis, peritoneal dialysis and renal transplantation. For haemodialysis to commence a permanent arteriovenous access (AVA) must be obtained. AVA can be achieved with either an arteriovenous fistula (AVF) or an arteriovenous graft (AVG). Where feasible an AVF is favoured because of a reduced risk of infection and higher patency rates [1].

An AVF can be complicated by thrombosis, stenosis, steal syndrome, low or high flow and arteriovenous fistula aneurysm (AVFA). In comparison to other AVF complications, aneurysm formation is not uncommon but it has a poorly described evidence base.

Definition

A true aneurysm has been defined by The Society for Vascular Surgery as a focal dilatation of intimal, medial and adventitial layers of the vessel wall [2]. The most recent Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines defined a true aneurysm as an abnormal blood-filled dilation of the blood vessel wall secondary to disease of the vessel wall [1].

In contrast, a pseudoaneurysm is defined by The Society for Vascular Surgery as a focal dilatation of the vessel wall by neointimal and fibrous tissue [2]. The description of a pseudoaneurysm by K/DOQI is a vascular abnormality that appears like an aneurysm but is lined by external fibrous tissue as opposed to a true vessel wall [1]. Guidelines from the Vascular Access Society regarding the definitions of aneurysms and pseudoaneurysms have not yet been formulated [3].

In terms of aneurysm size, current guidelines offer no strict criteria to define and classify AVFA. The suggested diameter of a usable AVF is 6 mm in the K/DOQI guidelines [1], which is three times greater than the diameter of a typical autologous vein [4,5]. In the published literature, the reported sizes of AVFA range between 19.5 and 80 mm, which encompass a more than threefold expansion of the advocated diameter of an AVF vein. As such, Valenti et al. [6] defined AVFA as any segment of vein with a diameter greater than 18 mm and Balaz et al. [7] proposed a definition of AVFA as a dilatation of all three vein layers to at least a diameter of 18 mm. This denotes an increase of the diameter of a vein in a maturated AVF by three times (3×6 mm = 18 mm).

Classification

To our knowledge, there are just a couple of classification systems for AVFA that have been reported to date: one by Valenti et al. [6] constructed from their own clinical findings and one by Balaz et al. [7] based on a review of published evidence.

Depending on the shape of the aneurysm Valenti et al. [6] categorised AVFAs into four different groups:

Type 1: Without a ''camel hump''
- 1a: dilatation lengthways along the vein; the vein is uniformly dilated from the site of the arterial anastomosis along the majority or all of its length. The configuration is akin to a hosepipe.
- 1b: An aneurysm after the anastomosis; the vein is dilated proximally. This type of aneurysm is usually within 5 cm of the arterial anastomosis.

Type 2: With a ''camel hump''

- 2a: The classic ''camel hump''; there is at least one localised venous dilatation. However, more frequently there are two. Hence, the description of a classic ''camel hump''. These dilatations emerge at cannulation sites from previous dialysis sessions. The vein is normal calibre between the locations of the aneurysms but can be stenosed.
- 2b: A mixture of types 2a and 1b; in other words, a post-anastomotic aneurysm with localised dilations.

Type 3: This class signifies aneurysms that do not have a typical configuration compatible with the description of either type 1 or type 2 AVFAs.
Type 4: These AVFAs clinically appear to be true localised aneurysms but a diagnosis of false aneurysm is confirmed on subsequent duplex imaging.

Balaz et al. [7] described a classification AVA aneurysms on the basis of the type of aneurysm. Depending on the presence of stenosis or thrombosis on ultrasound or fistulography, Balaz et al. [7] classified the type of AVA into four groups:

Type I – No evidence of stenosis or thrombosis.

Type II – Significant (≥50%) stenosis in the arterial inflow vessel (A), at the site of the arterial anastomosis (B), along the area used for cannulation (C), or in the central venous system (D).
Type III – Incomplete thrombosis with at least 50% occlusion of the lumen.
Type IV – A complete thrombosis.

The others parameter as: (a) aneurysm diameter (b) whether there was a arteriovenous graft or AVF (c) the type of vein that is aneurysmal (d) the amount of aneurysms are recommended for detailed description of aneurysm degeneration of AVA according to the suggested nomenclature in the clinical practice recommendation [8].

Both classification systems are important, even though Valenti's is focused on morphology and should be assessed in outpatient clinic without ultrasound. However, this system does not include intravenous pathology. On the other hand, Balaz's system does not describe shape of aneurysm but describes presence of stenosis or/and thrombosis, which is important for treatment strategy. For detailed description of AVFA, the combination of both systems seems to be logical and interesting solution.

Prevalence and aetiology

In the published literature, the rate of aneurysm development in the haemodialysis population varies widely from 6% up to 60% [6,9–11]. However, these figures are not truly representative, as inconsistencies in the definition of true aneurysms, false aneurysms and pseudoaneurysms in different studies mean that these figures represent the total occurrence of all types aneurysms.

The underlying pathogenesis of AVFA development has not been conclusively proven but several theories exist. In the immediate period following AVF surgery there is geometric and haemodynamic maturation that represents the origin of AVFA development. Flow volumes escalate through the AVF due to the pressure differences between the arterial and venous circulation [12]. Resistance in the venous outflow and capacity of the vein to distend facilitates the arterialised vein to cope with high flow rates under reduced pressure gradients [13]. As a result of arterial pressure, the venous component of the AVF distends both laterally and distally but crucially not in the axial direction, which leads to a convoluted conformation [14].

Furthermore, increased venous pressure may also result from stenosis within the central venous system and hasten aneurysm formation. Central venous stenosis typically results from extended central venous catheterisation and previously published studies suggest a broad range of incidence between 13% and 100% [15–20]. Imaging of the central venous system by fistulography or ultrasound is not routine however, and potentially explains the wide incidence rates reported. Finally, repeated venepuncture during regular dialysis sessions can lead to localised tissue damage, trauma, inflammation and infection resulting in injury of the vessel wall and subsequent aneurysmal defects [21].

Clinical presentation and management of arteriovenous aneurysm

Many patients consider AVFA a distressing cosmetic issue but in the absence of symptoms a line of conservative management can be safely adopted. This is an approach advocated by K/DOQI, who recommend conservative management consisting of avoidance of cannulation of aneurysmal areas in patients with an asymptomatic AVFA [1]. To facilitate use of fistulae with aneurysmal dilatations for dialysis a modified buttonhole cannulation technique has also been described [22].

However, additional specific guidance on when and how to treat AVFA in symptomatic patients is currently unavailable [1–3]. Symptomatic AVFA can present with discomfort, protracted bleeding after dialysis, low flow and inadequate dialysis or high flow with risk of steal syndrome or high output cardiac failure. Bleeding can also occur from rupture of the aneurysm when skin over the aneurysm becomes progressively thin, necrotic or gets infected.

A review of the literature reveals that important considerations in the management of AVFA include the condition of overlying skin, presence or absence of symptoms, difficulty with cannulation, and performance of the AVA. To facilitate clinical decision-making, measurements of access flow, cardiac output and cardiac index by Doppler ultrasound and echocardiography should be obtained. When considered in isolation, the diameter of the aneurysm and cosmetic considerations of the patient are not indications for intervention. The four main groups of clinical presentations of AVFA are discussed further below.

Group A – patient discomfort or cosmetic concerns

Pain and cosmetic problems can arise in all types AVFA described in the classification system of Balaz et al. [7]. Discomfort around the AVFA is an infrequent symptom and

alternative sources of pain should first be excluded before attributing symptoms of pain to the aneurysm. Pain can result from peripheral nerve compression by the aneurysm but this diagnosis is made more complex by the frequency of associated uraemic or diabetic polyneuropathy in the haemodialysis population [23]. Issues related to cosmetics from the AVFA are subjective in nature and are generally not considered an indication for intervention. If operative intervention is considered for an otherwise asymptomatic aneurysm on the basis of cosmetics, this decision must be weighed carefully against potential post-operative complications. The risks of intervention including bleeding, thrombosis and loss of access should be explicitly explained to the patient.

Group B – risk of bleeding

With the exception of type IV AVFA, bleeding may occur in all types of AVFA in the classification system of Balaz et al. [7]. Aneurysmal bleeding may result from rupture or trauma but most often it occurs more indolently at the conclusion of a dialysis session following removal of the haemodialysis needle. Factors that increase the risk of bleeding include degradation of the skin, brisk expansion of the aneurysm, high blood pressure, intra-access pressure and use of anticoagulants. If these warning signs exist or the patient is actively bleeding, immediate intervention is required.

Group C – low flow issues

Low flow occurs in Balaz et al. type II and type III AVFA [7]. Low flow resulting from impaired arterial inflow or venous outflow stenosis leads to inadequate dialysis. A haemodynamically significant venous outflow stenosis is usually defined on angiography or ultrasonography as greater than 50% reduction in vessel diameter [1]. Treatment of AVFA with low flow aims to address the stenosis, usually by means of angioplasty of the stenosis in the first instance. If concomitant stenoses with the aforementioned high-risk features for bleeding are present then an open surgical approach is recommended.

Group D – high flow issues with steal syndrome or risk of high output cardiac failure

Distal perfusion may become compromised by a high flow AVFA or high-output cardiac failure may result, particularly in patients with coronary artery disease [24]. Ischaemia of the hand, known as high flow steal syndrome, can also be caused by stenosis proximal or distal to the access anastomosis. However, this article focuses on steal syndrome secondary to high flow. Although it should be noted that steal syndrome is not always accompanied by aneurysm formation.

Steal syndrome

Steal syndrome can be graded from 0 to 3 [8]:

Grade 0: No steal present.

Grade 1: Mild – peripheral coolness, minimal symptoms, augmented flow with occlusion of access.

Grade 2: Moderate – intermittent ischaemia only during dialysis sessions or claudication.

Grade 3: Severe – ischaemic rest pain or loss of tissue.

Steal syndrome is a potentially limb threatening complication and if it is clinically significant it should be promptly diagnosed with a view to rapid treatment. The objectives of managing steal syndrome are re-establishment of antegrade flow to maintain distal perfusion and safeguard use of the AVA for dialysis. A cut-off value for when the high flow AVF presents a significant risk for the development of steal syndrome has not been clearly defined. Intervention is occasionally needed for grade 2 steal syndrome and obligatory for grade 3 steal syndrome.

High output cardiac failure

An AVFA with high flow may result in substantial increase in cardiac index, heart re-modelling secondary to volume overload and congestive cardiac failure [25,26]. Clinical signs consistent with systemic or pulmonary congestion accompanied by a cardiac output >8 L/min or cardiac index >3.9 L/min/m^2 is an accepted definition of high output cardiac failure [27].

The majority of AVA have an upper limit of flow of 2.5 L/min, which surpasses the flow required to produce reversible symptoms [28]. In a study of stable patients on long-term haemodialysis, Pandeya et al. presented the notion of cardiopulmonary recirculation using the ratio of access flow rate/cardiac output [29]. They reported a mean access flow of 1.6 L/min and a mean cardiac output of 7.2 L/min, hence designating a mean cardiopulmonary recirculation of 22%. MacRae et al. [30] proposed that harmful effects of high access flow can occur when the access flow rate is higher than 3 L/min or when access flow rate/cardiac output is 30% or higher. Wijnen et al. [31] reported that access flow rate was significantly and positively associated to cardiac output and cardiac index, and inversely correlated to peripheral vascular resistance. However, when a high flow AVFA is at risk for the development of high output cardiac failure has not been specifically defined as yet and treatment guidelines are required.

Previous studies have demonstrated that AVF closure reduces left ventricular diameter and mass [32–34]. However, it is unclear what effect AVF reduction has on heart remodelling. In a published series of thirty patients with AVF flow ≥1.5 L/min treated by aneurysmorrhaphy with external mesh prosthesis, Wohlfahrt et al. [35] evaluated the effect of reduction of AVF flow on cardiac remodelling. Reverse cardiac remodelling (decreased LV end-diastolic diameter and mass, left atrial and right ventricular diameter and pulmonary pressure) was observed only in patients with elevated cardiac index (≥3.9 L/min/m^2). The study concluded that the effect of AVF reduction on heart remodelling is dependent on the pre-operative cardiac index and not on the access flow rate. This study therefore intimates that increased cardiac index may be the most significant factor to consider when contemplating AVF reduction techniques in patients with a high flow AVF. As such, in the majority of patients, AVF reduction/closure may not be required and intervention can be reserved for patients

who develop adverse cardiac remodelling or congestive cardiac failure.

It is thus our recommendation that treatment should be offered to all patients with access flow rate >2.5 L/min who have either stage C or stage D heart failure as described by the American College of Cardiology/American Heart Association (ACC/AHA) [36]. In terms of pre-emptive treatment in asymptomatic patients, our recommendation is to intervene in patients with a high flow AVFA only when either there is an access flow rate >3.0 L/min or cardiopulmonary recirculation ≥30% or cardiac index >3.9 L/min/m^2. Conversely, no intervention is required in asymptomatic patients with high flow AVFA with normal cardiac index and no LV dilation.

Techniques for the treatment of arteriovenous aneurysm

Various techniques for treating symptomatic AVFA have been described in the literature. The principle methods of surgical intervention are resection with substitution, remodelling techniques and ligation. Stent grafting is the endovascular technique of choice. However, despite the array of options available, the majority of these techniques have only been reported as individual case studies or small case series. Furthermore, to date none of the described techniques have been scrutinised in a head to head fashion, either in a randomised control trial or prospective non-randomised study.

Resection and/or substitution techniques

Resecting the aneurysmal component of the AVF and forming a fresh anastomosis more proximally can deal with post-anastomotic aneurysms situated within a short venous segment. All types of AVFA can be managed in this fashion, even those with thrombosis. However, the proximal and distal venous segments must be free from thrombosis to allow construction of an anastomosis either in an end-to-end or end-to-side fashion. The principle benefit of this approach is that a healthy section of vein is available straightaway for use in dialysis. If a substitution is required, either prosthetic material or autologous vein (e.g. great saphenous vein) can be utilised. Prosthetic conduits have the advantage that they can be cannulated earlier than autogenous grafts but they carry a higher risk of infection and thrombosis. When using substitution techniques, either with prosthetic or venous conduits, 12-month patency rates of 47–100% have been reported [37,20,38].

Remodelling techniques

There are a variety of remodelling techniques (aneurysmorrhaphy, reinforced aneurysmorrhaphy, plication) that utilise native vein to maintain the character of the fistula. One method is aneurysmorrhaphy, which involves resection of part of the aneurysm sac. Another method is reinforced aneurysmorrhaphy, which involves resection of the aneurysm and supporting parts of the vein followed by mesh external prosthesis. The rationale for implantation of external mesh prosthesis on the surface of the vein to be repaired is that it reportedly reduces shear stress on the wall of the vein. This could result in less turbulent blood flow, endothelial injury, and thrombus formation [39,40]. Balaz et al. [41] first reported the reinforced aneurysmorrhaphy with polyester mesh tube. This novel approach is feasible to treat multiple extensive AVFAs but since cannulation of the repaired fistulae has to be delayed for 4–6 weeks of recovery a temporary tunnelled dialysis catheter is needed. The 1-year primary patency results of remodelling techniques with and without support appear similar (86% [42] vs. 80–93% [19,43]). Primary patency rates of 88%, 84%, and 69% at 1, 2, and 3 years, respectively have also been reported using stapled aneurysmorrhaphy [18]. Going forward there is a need for comparative studies to assess the efficacy of different aneurysmorrhaphy techniques as well as the need for external support.

Endovascular techniques

In keeping with the upsurge in endovascular techniques in vascular surgery in general there has been an emergence of endovascular approaches to vascular access problems. First reported in 2002 [44], proponents of covered stent graft insertion to treat AVFAs, cite the fact that the procedure can be performed on an outpatient basis and does not require interruption of dialysis since early venepuncture is still possible [45,46]. In a patient with active bleeding, treatment with an endovascular stent graft can also secure haemostasis. Although the reported one year patency rates of 87% [16] are comparable to the previously described remodelling techniques, criticism of stent graft insertion centre on the increased costs of the procedure and lack of utility in specific subgroups of patients. For instance, situations where the endovascular approach is not suitable include patients with aneurysms close to the anastomosis, steal syndrome and large aneurysms lacking an adequate landing zone for sealing the stent graft.

Surgical techniques for high flow AVFA

Treatment options are similar for steal syndrome and high output cardiac failure. These include flow-limiting procedures (e.g. plication, banding and minimally invasive limited ligation endoluminal-assisted revision (MILLER)), distal revascularization with interval ligation (DRIL), proximalization of arterial inflow (PAI), revascularization using distal inflow (RUDI), transposition of radial artery, proximal radial artery ligation (PRAL) and ligation of the AVF.

While several studies have reported on the treatment of high flow vascular access, only a few of them assess high flow vascular access in the presence of an aneurysm. Aneurysmorrhaphy with external mesh can significantly reduce flow rates [43,35] and precipitate reverse cardiac remodelling with flow rates ≥1.5 L/min in patients with elevated cardiac index (≥3.9 L/min/m^2) [35]. However, aneurysmorrhaphy has proven unsuccessful with flow rates >2.5 L/min [19]. Therefore our recommendation is that for high flow AVFA sites in the upper arm, aneurysmorrhaphy and anastomosis relocation to forearm arteries is performed, with aneurysmorrhaphy and reduction of the anastomosis used for those sited in the forearm.

Ligation

Ligation is technically straightforward, and can successfully treat steal syndrome or high output cardiac failure but unlike surgical revision techniques, it does not preserve vascular access. When other revision techniques have failed, ligation should be considered as a last option. Haemorrhage from an AVFA is a potentially fatal complication [47], and if acute bleeding is associated with haemorrhagic shock then immediate ligation of the AVF should be performed, with reconstruction deferred until after the patient has recovered. A further indication for ligation is a high flow AVFA in patients who have received a kidney transplant with expected good long-term graft function.

Summary

An AVFA is defined by an enlargement of all three vessel layers to a diameter greater than 18 mm. In asymptomatic patients conservative management is appropriate. The principle indications for intervention in symptomatic patients are pain, bleeding prevention and low or high flow. The diameter of AVFA and issues purely related to cosmetics are not indications for intervention. Despite a lack of strong evidence base concerning which surgical treatment option is optimal, in order to preserve the nature of the AVF we recommend techniques utilising the native vein as first-line. According to the literature, the best long-term results are achieved by using aneurysmorrhaphy with or without a prosthetic support. Insertion of a stent graft or ligation of AVFA is recommended for emergent treatment in actively bleeding patients.

Conflict of interest

None declared.

Ethical statement

Authors state that the research was conducted according to ethical standards.

Funding body

None.

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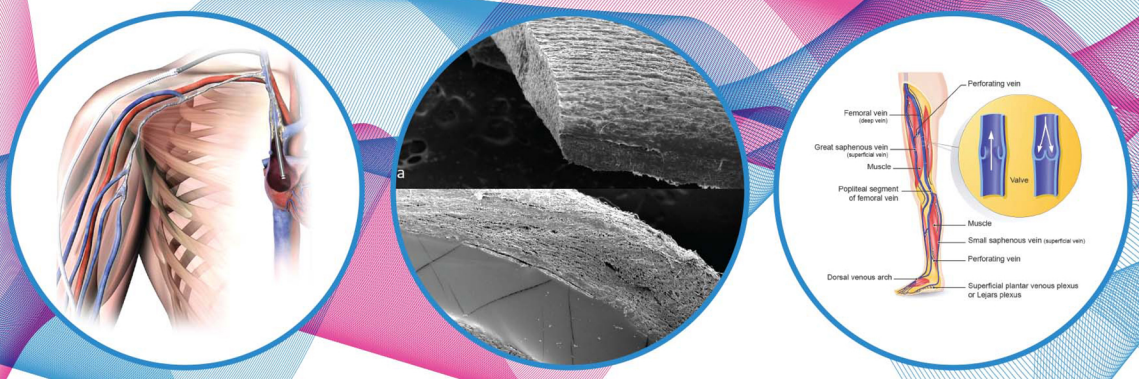

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INNOVATIONS IN DIALYSIS VASCULAR ACCESS SURGERY

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In: Innovations in Dialysis Vascular Access Surgery
Editor: Archil B. Chkhotua
ISBN: 978-1-53612-158-2

Chapter 26

ARTERIOVENOUS FISTULA ANEURYSM

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ABSTRACT

The incidence of aneurysms of arteriovenous fistula in haemodialysis patients is reported to be as high as 60%. Although the clinical presentation of arteriovenous fistula aneurysm is often asymptomatic, symptomatic cases should be associated with serious complications. Despite the development of various surgical and endovascular procedures to treat arteriovenous fistula aneurysms, clinical guidelines are limited in terms of when and how to intervene. The objective of this chapter is to discuss the definition, aetiology, classification, clinical presentation, indications and methods for treatment of arteriovenous fistula aneurysm.

The authors' experience and a non-systematic literature review of articles published between January 1973 and June 2016 were used as the source of information for this chapter. Databases searched include Medline, Science direct, Scopus and the Cochrane Database of Systematic Reviews. Eligibility criteria were aneurysm of arteriovenous fistula and treatment techniques. Information regarding aneurysms and pseudoaneurysms involving prosthetic arteriovenous access were not included in this chapter.

Indications for treatment of arteriovenous fistula aneurysm are patient discomfort, bleeding prevention and low or high flow. The diameter of the arteriovenous fistula aneurysm is not a sole indication for treatment. The most frequently used techniques for treating arteriovenous fistula aneurysm are resection with interposition, remodelling and stentgraft implantation.

Arteriovenous fistula aneurysm is characterized by an enlargement of all three vessel layers to a diameter of more than 18 mm. In asymptomatic aneurysms, conservative

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treatment is recommended. The main indications for treatment of a symptomatic aneurysm are patient discomfort, bleeding prevention and low or high flow. The diameter of an arteriovenous fistula aneurysm and cosmetic issues should not be used as the sole indications for treatment. Although various surgical and endovascular techniques have been described, no prospective comparative study between these techniques exists and no particular method is recommended.

Keywords: aneurysm, arteriovenous fistula, haemodialysis, treatment

INTRODUCTION

Treatment options for patients with chronic renal failure include haemodialysis, peritoneal dialysis and kidney transplantation. Haemodialysis requires permanent arteriovenous access (AVA), which can be obtained through an arteriovenous fistula (AVF) or arteriovenous graft (AVG), with the former being preferred due to its lower rate of infection and higher patency rate [1].

There are several complications of AVF. These include thrombosis, stenosis, steal syndrome, low or high flow and last, but not least, arteriovenous fistula aneurysm (AVFA). In contrast to the other clearly described vascular access complications, aneurysm formation is not rare and is under-reported in literature.

The clinical presentation of AVFA is often asymptomatic and does not require any intervention. Indications for treatment and type of intervention vary among authors. There still does not seem to be any one technique that evidently stands out from the rest and treatment preferences vary between different surgeons and treatment centres. This heterogeneity results from the insufficiency of the current international guidelines (K/DOQI-Kidney Disease Outcomes Quality Initiative, SVS-Society of Vascular Surgery North-America, VAS-Vascular Access Society) regarding arteriovenous fistula aneurysm [1-3].

The objective of this chapter is to discuss the definition, aetiology, classification, clinical presentation and indications and techniques for treatment of AVFA.

DEFINITION OF ARTERIOVENOUS FISTULA ANEURYSM

The Society for Vascular Surgery defines a true aneurysm as a focal dilatation of all three vessel layers and a pseudoaneurysm as a focal dilatation of the vessel wall by neointimal and fibrous tissue [2]. In the current K/DOQI guidelines an aneurysm is defined as an abnormal blood-filled dilation of the blood vessel wall resulting from disease of the vessel wall and a pseudoaneurysm is defined as a vascular abnormality that resembles an aneurysm but is lined by external fibrous tissue rather than a true vessel wall [1]. In the current guidelines of the Vascular Access Society, definitions of aneurysms and pseudoaneurysms are lacking [3].

Vesely TM, recommended using the term aneurysm for the autologous arteriovenous access only when the etiological factor is showing increased intraluminal pressure due to distal stenosis and term pseudoaneurysm is limited for the cases when aetiology is degeneration of the vein wall, from repeated cannulation [4]. Even though this definition seems logical, it is difficult to use in clinical practice as both etiological factors are often present simultaneously [5].

Table 1. Retrospective studies which describe the treatment of AVFA (AVFA – arteriovenous fistula aneurysm, AVF – arteriovenous fistula, AVG – arteriovenous graft, pp- primary patency, as-assisted primary patency, sp- secondary patency, m- months), studies with arteriovenous graft pseudoaneurysms only were excluded

Author	Year published	N°pts	Size criterion of aneurysm	Aneurysm diameter (mm)	Forearm location	Upper arm location	Other location	Treatment techniques	Follow up (months)	Patency (duration)
DuBose et al. [43]	2016	15	---	---	2	13	---	Resection and repair with tubularized extracellular matrix patch or tube interposition	mean 6,9	pp 87% (6,9 m)
Vo et al. [20]	2015	40	2x the diameter of the normal adjacent vein	45	13	27	---	Staple aneurysmorrhaphy	median 20 (5-81)	as 69% (36 m) sp 85% (36 m)
Powell et al. [55]	2015	35	---	---	5	30	---	Long segment plication with or without segmental vein resection	1,0	pp 88% (1m)
Furukawa [63]	2015	23 AVF 3 AVG	Dilatation of more than 3x the diameter of native vessels	29,8 ± 8.0	23	1	2	Resection only (n = 7)/plication (n = 1)/resection and new AVF/AVG creation (n = 18)	1,0	100% (1m)
Patel et al. [19]	2015	48	---	---	7	41	---	Aneurysmorrhaphy	<12	100% (<12 m)
Piccolo et al. [59]	2015	10	---	36,3	1	9	---	Aneurysmorrhaphy with the thoracoabdominal stapler	mean 11 (4–27)	pp 80% (6 m) as 90% (6 m)
Tozzi et al. [64]	2014	14	more than 15mm	24,7	7	7	---	Stapled aneurysmectomy	median 16.5 (14- 23)	pp 85,7% (16,5m)
Sigala et al. [56]	2014	31	---	---	11	20	---	Resection with end-to-end anastomosis (n = 5)/ aneurysmorrhaphy (n = 26)	25 ± 14/33 ± 13	pp 81% (24m) sp 90% (24m)
Cingoz et al. [42]	2014	28	---	40 ± 12	3	25	---	Resection and repair with interposition grafting	mean 37.3 ± 2.8	100%/36
Belli et al. [54]	2014	31	---	---	7	22	2	Excision, repair with primary suturing (n = 14)/interposition grafting (n = 12)/ligation (n = 5)	mean 16 (1-69)	44%/24
Rokosny et al. [50]	2014	62	3x larger diameter than other venous segments from the access site	34.47 ± 7.33	40	22	---	Aneurysmorrhaphy with external PTFE mesh	mean 14.66 ± 12.80	pp 79% (12m) as 80% (12m)

Table 1. (Continued)

Author	Year published	N°pts	Size criterion of aneurysm	Aneurysm diameter (mm)	Forearm location	Upper arm location	Other location	Treatment techniques	Follow up (months)	Patency (duration)
Hossny [53]	2014	14	---	53 ± 16	5	9	---	Partial aneurysmectomy	mean 30,4 ± 14,4 (6-48)	85,7% (12m) 64,3% (24m)
Zink et al. [65]	2013	17 AVF 21 AVG	2x greater diameter than remainder of access	---	6	32	---	Stentgrafting	median 7,1	pp 47,4% (6m) as 76,3% (6m)
Kinning et al. [66]	2013	4 AVF 20 AVG	---	---	0 AVF 1 AVG	4 AVF 18 AVG	0 AVF 1 AVG	Stentgrafting	mean 17,6 (0-76)	as 54% (6m) as 50% (12m)
Almehmi et al. [45]	2012	36	---	---	10	26	---	Partial aneurysmectomy	mean 7.1 ± 4.8 (2–18)	pp 56% (6m) ap 97% (6m)
Shah et al. [67]	2012	11 AVF 13 AVG	---	19.5 ± 10	---	---	---	Stentgrafting (with simultaneous open surgical decompression n = 2)	mean 8,9 median 3,3	69% (5m)
Belli et al. [68]	2012	26 AVF 5 AVG	---	26 ± 9.3 (AVF) 34 ± 15,8 (AVG)	7 AVF 2 AVG	19 AVF 1 AVG	0 AVF 2 AVG	Excision and repair with primary suturing (n = 14), end-to-end anastomosis (n = 4) vein (n = 4)/prosthesis (n = 4) interposition, ligation (n = 5)	mean 14 (0-57)	pp 52% (12m)
Bachleda et al. [69]	2011	11	---	---	---	---	---	Ligation (n = 2), resection and interposition grafting (n = 3), partial aneurysmectomy (n = 6)	mean 17 (5-32)	---
Ekim et al. [70]	2011	20	---	55.2 ± 17.3	2	18	---	Plication (n = 17)/excision and graft interposition (n = 2)/resection (n = 1)	mean 26 (2-38)	---
Pasklinsky et al. [22]	2011	23	3x larger diameter than autologous vessel/ more than 20mm	33	10	13	---	Excision and aneurysm repair with vein (n = 7)/prosthesis (n = 3) Ligation with (n = 7) or without (n = 6) excision	median 19 (8-25)	57.1% (18 m) for vein/33.3% (25m) for PTFE interposition
Shemesh et al. [18]	2011	11 AVF 9 AVG	---	30± 9	4	16	---	Stentgrafting	median 15 (6.3 -55.5)	87% (12m)
Karatepe et al. [71]	2011	30	more than 40mm	40 or more	21	7	---	Plication (n = 25), Excision an graft interposition (3), stenting (n = 2)	mean 12	100% (6m)
Berard et al.	2010	33	3x larger diameter	25-60	17	16	---	Aneurysmorrhaphy with PTFE mesh	mean 12 (4-	ap93% (12m)

Author	Year published	N°pts	Size criterion of aneurysm	Aneurysm diameter (mm)	Forearm location	Upper arm location	Other location	Treatment techniques	Follow up (months)	Patency (duration)
[21]			than other venous segments from the access site						22)	
Woo et al. [52]	2010	19	---	40-70	3	16	---	Partial aneurysmectomy	median 23, IQR 22	pp 92.2% (12m) sp 100% (12m)
Georgiadis et al. [41]	2008	26 AVF 18 AVG	---	36,4 (20-80)	23	21	---	Primary repair (n = 4), excision and graft interposition (n = 29)/new AVF (n = 7)/bypass (n = 4), partial resection (n = 1)	mean 20,38 ± 17,03 (2,0-70,5)	69 ± 9% (12m) for AVF, 39 ± 11% (12m) for AVG
Balaz et al. [46]	2008	4	---	---	4	0	---	Aneurysmorrhaphy with external PTFE mesh	---	---
Shojaiefard et al. [72]	2007	22	---	---	11	11	---	Partial aneurysmectomy	mean 15 (9-18)	93,7% (15m)
Lo et al. [73]	2007	15	---	---	---	---	---	Plication	---	---
Pierce et al. [58]	2007	12	---	28.1 ± 7,3	8	4	---	Aneurysmorrhaphy with stapler	36 ± 28	---
Karabay et al. [74]	2004	18	---	---	15	3	---	Partial aneurysmectomy	mean 29,1 (7-50)	100% (6m)
Najibi et al. [75]	2002	2 AVF 8 AVG	---	30 (13-50)	3	7	---	Stentgrafting	6 (5-7)	---
Cavallaro et al. [76]	2000	26	---	---	26	0	---	Resection and reanastomis of the stump/ creation of new fistula	8	---
Hakim et al. [57]	1997	6	---	---	1	5	---	Aneurysmorrhaphy with stapler	range 8-12	---

No precise size criteria to define and classify AVFA are given in the current guidelines. Most reports have defined AVFA based upon size (Table 1). According to the K/DOQI guidelines, the recommended diameter of a usable AVF is 6 mm [1], three times larger than the diameter of a normal autologous vein [6, 7]. On review of the literature, the size of AVFA vary between 19.5 and 80 mm (Table 1), which represents more than three times the enlargement of the recommended diameter of an arteriovenous fistula vein. On the basis of these findings Balaz et al. suggested defining AVFA as a dilatation of all three vein layers with a minimal diameter of 18 mm. This represents a threefold enlargement of the diameter of a vein in a maturated AVF (3 × 6 mm = 18 mm) [5].

Prevalence and Aetiology of Arteriovenous Fistula Aneurysm

In studies of haemodialysis patients, the frequency of aneurysm formation varies considerably, between 6% and 60%. However, these figures represent the total occurrence of true aneurysms, false aneurysms and pseudoaneurysms as different authors define aneurysms differently [8-11].

While the exact pathogenesis of aneurysm formation is not fully understood, several mechanisms have been proposed. The process of AVFA probably starts at the time of the creation of the AVF, as it undergoes geometric and hemodynamic maturation. The cephalic vein and the brachial artery increased their diameter from 2.29 to 6.31 mm, and from 3.76 to 5.39 mm, respectively, over an eight-week period after the surgery [12].

The AVF thus generates a large pressure gradient between the high-pressure inflow artery and the low-resistance outflow vein, which increases flow volume through the fistula [13]. The combination of low venous outflow resistance and the great ability of the venous wall to distend makes the arterialized vein capable of creating high flow rates under low pressure gradients [14]. Thus, the venous arm of the fistula becomes tortuous under the arterial pressure as distension occurs both laterally and distally and it is not stretched axially [15]. Another effect of the high blood flow in the vein is venous wall re-modelling [16]. A physical explanation of this situation is well described by Laplace's law ($T = P.R/t$, T - wall tension, P - pressure, R - radius of the vessel, t - vessel thickness), which states that wall tension is directly related to the radius of the vessel and intra-vessel pressure. Additionally, as the vessel dilates and the diameter enlarges, the wall tension increases, causing further vein dilation.

Central vein stenosis, usually occurring as a result of prolonged central venous catheterization, is another hemodynamic factor leading to increased venous pressure and thus accelerating aneurysm formation. In a study by Rajput et al., 78% of patients with symptomatic arteriovenous access aneurysms, defined as a focal dilatation of the outflow vein diameter greater than two times the normal calibre of the adjacent normal fistula vein segment, had central vein stenosis requiring angioplasty [17]. In a study by Shemesh et al. all patients (n = 20) with AVA aneurysms treated with stent graft had central vein stenosis [18]. Patel et al. published a study of 48 patients treated by aneurysmorrhaphy, in which at least one venous outflow stenosis needing balloon angioplasty was found in 90% of patients [19]. Vo et al. treated 40 AVFA by aneurysmorrhaphy with a staple, detected proximal venous outflow stenosis in 19 of 40 AVFs (48%) preoperatively and in 11 of 38 AVFs (29%)

postoperatively [20]. On the other hand, Berard et al. [21] in a cohort of 38 patients found concomitant central vein stenosis in only five patients (13%), and Pasklinsky et al. [22] reported 23 patients of whom four (17%) were found to have outflow vein stenosis. This discrepancy may be due to the fact that fistulography and assessment of the central venous system is not routinely performed in all patients, but only in candidates for stent grafting or if pre-operative ultrasound assessment demonstrates an impairment of the fistula outflow due to the central vein stenosis.

Local irritation of the vein wall as a result of repeated needle puncture of the fistula during dialysis therapy causes local tissue injury, necrosis and scarring, resulting in fistula enlargement, moreover, inflammation or infection of the puncture sites could aggravate these local changes leading to further wall damage and defects [23].This small tissue defect in the cannulated part of the vein is sealed by fibrin plugs and subsequently replaced by connective tissue, which accumulates, expanding the circumference of the puncture segments.

Classification of Arteriovenous Fistula Aneurysms

As far as we are aware, two classification systems for AVFA have been published: one by Valenti et al. [11] based on their own clinical findings and one by Balaz et al. [5] based on a literature review.

Valenti et al. classified AVFAs into four groups according to the shape of aneurysm [11]. Bleeding risk was assessed for each type of aneurysm, which was used to suggest management strategies. Aneurysms with a ‘‘camel hump‘‘ appearance comprise group 2. Aneurysms without a ‘‘camel hump‘‘ appearance comprise group 1. Both groups (1 and 2) are further divided into two subgroups. Group 3 consists of miscellaneous unclassifiable AVFAs and group 4 consists of false aneurysms (Figure 1).

Type 1: without ‘‘camel hump’’

- 1a: dilated along the length of the vein; the vein is dilated almost uniformly from the arterial anastomosis along most, if not all of its length. The appearance resembles a hose pipe.
- 1b: postanastomotic aneurysm; the proximal part of the vein is dilated. This is almost always seen within 5 cm of the arterial anastomosis.

Type 2: with ‘‘camel hump’’;

- 2a: the classic ‘‘camel hump’’. There is at least one localised dilatation of the vein, but more often two. This is the classic camel hump. These dilatations appear to correlate with sites of needling for dialysis. Between the aneurysms the vein remains at its normal calibre, or, in some cases, is stenosed.
- 2b: a combination of types 2a and 1b. This is a post anastomotic aneurysm with localised dilations.

Type 3: These represent AVFAs, which do not fit the groups above and bare no resemblance to each other.

Type 4: These may appear to be true localised aneurysms but on duplex testing are proven to be false aneurysms.

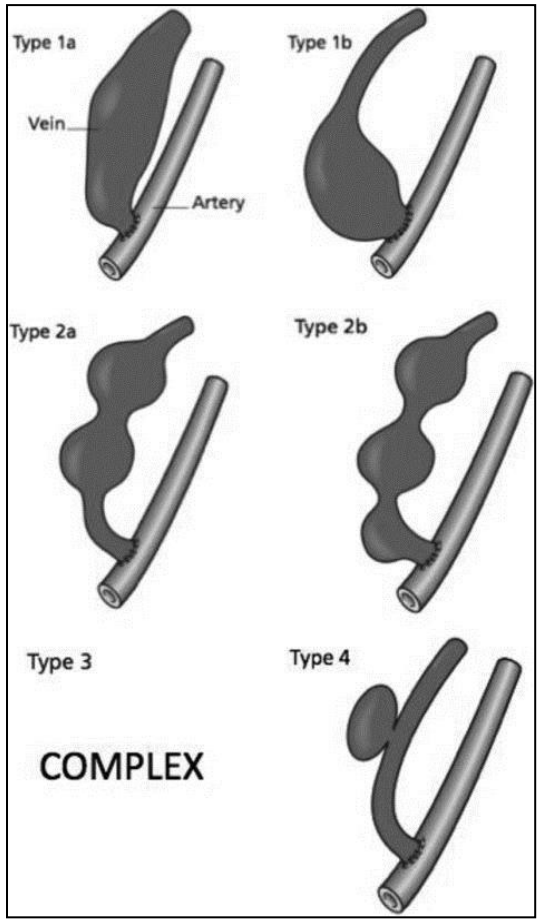

Figure 1. Classification system for autogenous arteriovenous fistula aneurysms [11].

The authors found that in a cohort of 292 dialyzed patients 43.5% presented with AVFA in the 2-year follow-up period. Six of them needed emergency surgery for bleeding, five of which were type 2 aneurysms. They concluded that type 1 aneurysms are much commoner in patients who have not yet punctured their fistula and have a relatively innocuous course, although type 1a aneurysms should be monitored for high flow, but type 1b can probably be followed up less frequently. Type 2 aneurysm, associated with venepuncture, are at significant risk of rupture and need to be monitored for evidence of overlying skin thinning which if present should be treated prophylactically. Surprisingly, aneurysm size and flow rate do not appear to be useful prognostic information for rupture [11]. Finally, recommended treatment for type 3 and 4 was is missing.

Balaz et al. [5] suggested to use the following items to describe AVFA: (a) diameter of the aneurysm (b) the type of AVA (AVG or AVF), (c) the type of vein affected by the aneurysm, (c) number of aneurysms and (d) type of aneurysm. They defined the type of AVFA according to the presence of stenosis or thrombosis identified by ultrasonography or fistulography. Their classification divides AVFA into four types I-IV (Figure 2):

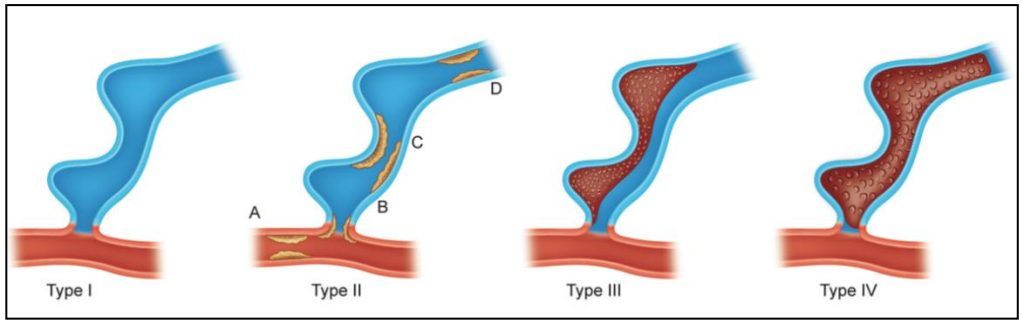

Figure 2. Classification of arteriovenous access aneurysm [5].

Type I – without stenosis and thrombosis
Type II – with hemodynamic significant stenosis (≥ 50%) in the inflow artery (A), at the arterial anastomosis (B), along the cannulation zone (C) or in the central vein (D)
Type III – with partial thrombosis occluding at least 50% of the lumen
Type IV – with complete thrombosis

Clinical Presentation of Arteriovenous Fistula Aneurysm

The clinical presentation of AVFA is usually asymptomatic and does not require any intervention, despite a lot of patients considering it a serious cosmetic issue. The clinical presentation of symptomatic AVFA includes pain, aneurysm rupture (resulting from thinning, necrosis, erosion and infection of the overlying skin), prolonged bleeding after dialysis, low flow (resulting in inadequate dialysis) and high flow (resulting in steal syndrome or high output cardiac failure). Four main groups of the clinical presentations of AVFA are recommended.

Group A - related to patient discomfort

This group includes pain and cosmetic issues. Pain in the region of an AVFA is a rare symptom, which may occur as a result of compression of a peripheral nerve by the aneurysm. Its differential diagnosis is complicated by the high incidence of concomitant uremic or diabetic polyneuropathy [24]. Cosmetic issues related to AVFA are highly subjective and are not recommended to be used as a sole indication for treatment. Both pain and cosmetic issues can be presented in all types of in the classification of AVFA proposed by Balaz et al. [5].

Group B - related to bleeding prevention

Bleeding from an AVFA is a severe and potentially lethal complication [25]. It most frequently occurs after removal of the haemodialysis needle, but can also occur after spontaneous rupture or traumatic injury. Predisposing factors for aneurysm bleeding include thinning or erosion of the overlying skin layer, compromised skin with or without inflammation, a rapidly expanding aneurysm, hypertension, intra-access pressure and

anticoagulation therapy. Bleeding can be present in all types of AVFA in the classification proposed by Balaz et al. [5], apart from type IV.

Group C – related to low flow

Low blood flow may result in inadequate dialysis and is caused by either impaired arterial inflow or venous outflow stenosis, which may occur between aneurysms, within the anastomotic area or in the central vein. The most commonly used parameter to define the hemodynamic relevance of stenosis is reduction in vessel diameter by more than 50% based on angiographic and/or ultrasonic findings [1]. Low flow is associated with aneurysm types II and III of the AVFA classification proposed by Balaz et al. [5] where hemodynamic significant stenosis (≥50%) is present.

Group D – related to high flow with steal syndrome or with the risk of high output cardiac failure

The major complications of high flow AVFA are distal hypoperfusion, which may lead to symptomatic hand ischaemia (high flow steal syndrome (SS)), and high-output cardiac failure (HOCF), which is more likely to occur in patients with coronary artery disease [26].

Although steal syndrome can be caused by stenosis of the arterial tree proximal to the access anastomosis (arterial inflow lesions) or arterial disease in the arterial tree distal to the access anastomosis (arterial outflow disease), this chapter is focused on high outflow steal syndrome. Steal syndrome is not always accompanied by aneurysm formation.

Steal syndrome can be graded from 0 to 3, as follows [27]:

Grade 0: No steal
Grade 1: Mild - cool extremity, few symptoms, flow augmentation with access occlusion
Grade 2: Moderate - intermittent ischemia only during dialysis, claudication
Grade 3: Severe -ischemic pain at rest, tissue loss

Another serious issue associated to AVFA with high flow is the risk of HOCF. Extremely elevated AVFA flow may lead to marked cardiac index elevation, volume overload-induced cardiac remodelling and clinical signs of heart failure [28, 29]. Generally, HOCF is defined as the combination of cardiac output (CO) greater than 8L/min or cardiac index greater than 9 L/min/m^2 with physical findings of systematic or pulmonary congestion [30]. Currently, there is no definition of when access flow (Qa) is too high. Although 2.5 L/min is the upper limit of flow in most AV access, this value exceeds that required to produce remediable symptoms in some reported cases [31]. The concept of using the ratio Qa/CO (cardiopulmonary recirculation - CPR) was proposed by Pandeya et al. in their study of stable long-term haemodialysed patients [32]. They found that the average Qa was 1.6 L/min and the average CO was 7.2 L/min, thus describing an average CPR of 22%. MacRae et al. suggested that the detrimental effect of high flow access on the cardiac function should be considered when the flow rate is greater than 3L/min or when Qa/CO is 30% or higher [33]. Wijnen et al. stated that Qa was significantly and positively related to CO and CI, and inversely related to peripheral vascular resistance (PVR) [34]. Recently Wohlfahrt et al. noted that increased cardiac index (>3.9L/min/m^2) in patients with high flow AVFA, but not increased

arteriovenous flow, may be the optimal parameter to assess when considering reduction techniques. Unfortunately, the precise definition when the high flow aneurysmatic AVF is a risk for the development of HOCF is not stated and appropriate guidelines are lacking [35].

INDICATION FOR TREATMENT OF ARTERIOVENOUS FISTULA ANEURYSM

The K/DOQI recommend that asymptomatic AVFA does not require intervention and can be managed by avoiding cannulation of the aneurysmatic areas [1]. However, further guidance on when and how to intervene in AVFA is lacking in the clinical guidelines [1-3].

Based on literature review, the management of AVFA is determined by assessment of the skin condition, clinical signs and symptoms, ease of cannulation, and functionality of the AVA. Doppler ultrasound and echocardiography assessment, including Qa, CO and CI measurement, should be mandatory and results must be carefully considered when making treatment decision. While the diameter of the aneurysms is a criterion for treatment of arterial aneurysms, it is not necessarily a criterion for the treatment of AVFA. Cosmetic issues, such as the diameter of the AVA aneurysm are not indications for treatment. The main indication for the treatment of an AVFA is its clinical presentation, which can be divided into the four groups discussed below.

Group A - related to patient discomfort

Pain in the region of the aneurysm is a rare symptom. Before considering surgical treatment of the aneurysm, other causes of the pain must be considered. Reconstruction of an AVFA for cosmetic reasons must be discussed in detail with the patient and all potential post-operative complications must be thoroughly explained. Generally, the cosmetic aspect alone in an otherwise asymptomatic aneurysm is not an indication for treatment.

Group B - related to bleeding prevention

In all patients with active bleeding and where the previously mentioned signs exist, immediate surgery is essential. In the case of acute bleeding associated with haemorrhagic shock, ligation of the AVF must be performed without delay, with reconstruction performed later after the patient has recovered.

Group C - related to low flow

Treatment of AVFA with low flow is focused on the lesion responsible for the low flow, which, in the first instance, would usually be by angioplasty of the stenosis in type II AVFA of the classification proposed by Balaz et al. [5]. When an aneurysm presents with both stenosis and a risk of bleeding an open surgical approach is recommended, although a covered stent with or without angioplasty can be used as an alternative. In type III AVFA of the Balaz et al. classification, resection of the aneurysm and replacement with a venous or prosthetic conduit or aneurysmorrhaphy is recommended [5].

Group D – related to high flow with the steal syndrome or with the risk of high output cardiac failure

High blood flow through an AVF with or without aneurysm formation is a serious complication that can result in high flow steal syndrome and high-output cardiac failure. Unfortunately, a cut-off value for when the high flow AVF presents a risk for the development of steal syndrome and HOCF has not been defined. These complications can be treated by ligating the AVF or surgical revision. Ligation is a simple and effect therapeutic option. However, unlike surgical revision, it does not preserve vascular access.

Steal syndrome is a potentially limb threatening event and must be diagnosed and treated without delay if it is clinically significant. The goals for treating steal syndrome are twofold: restoration of antegrade flow sufficient to maintain distal perfusion and maintenance of the AV access for dialysis. Intervention is sometimes necessary for grade 2 steal syndrome and mandatory for grade 3.

HOCF can be treated by closure or reducing the AVF. Several previous studies have shown that AVF closure decreases left ventricular diameter and mass [36-38]. However, the effect of AVF reduction on heart remodelling is unclear. Recently Wohlfahrt et al. published the first study evaluating the effect of reduction of AVF flow on heart remodelling on thirty patients with AVF flow $\geqslant$ 1.5 L min^{-1} treated by aneurysmorrhaphy with external mesh prosthesis [35]. Reduction of high flow AVF leads to reverse cardiac remodelling (decreased LV end-diastolic diameter and mass, left atrial and right ventricular diameter and pulmonary pressure), but only in patients with elevated CI ($\geqslant$ 3.9 L/min/m^2). The study concluded that the effect of AVF reduction on heart remodelling is dependent on cardiac index before the operation, but does not depend on increased AVF flow. This finding suggests that increased cardiac index, but not increased AVF flow, may be the most important parameter to assess when considering AVF reduction techniques in patients with high flow AVF. Thus, in most patients, AVF reduction/closure may not be required; intervention is required only among patients who develop adverse remodelling or heart failure.

At present, no precise criteria exist for the pre-emptive treatment of patients with a high flow AVF. We recommend treatment for all patients with Qa >2.5L/min who are in stage C (patients with current or past clinical heart failure) or in stage D (patients with end-stage refractory heart failure, who are candidates for extraordinary forms of therapy or for compassionate end-of-life care) classified according to the American College of Cardiology/American Heart Association (ACC/AHA) [39]. In asymptomatic patients, we recommend preemptive treatment of high flow AVFA when, Qa >3.0 L/min or Qa/CO $\geq$ 30% or cardiac index >3.9L/min/m^2. Patients with high flow AVFA with normal cardiac index, no LV dilation and without symptoms of heart failure do not require surgical flow reduction.

TREATMENT OF ARTERIOVENOUS FISTULA ANEURYSM

Conservative treatment is indicated if an AVFA is asymptomatic, it consists of avoiding aneurysmatic areas for cannulation [1] and using the modified buttonhole cannulation technique, which was proposed as a solution for fistulae with aneurysmal dilatations [40]. Treatment is recommended for all AVFA that are symptomatic, present with a risk of bleeding (indication group B), with low flow (indication group C) and in selected patients with high flow AVF (indication group D).

Although several interventions for symptomatic AVFA have been described in the literature (resection with substitution, remodelling techniques, stent grafting and ligation) most of these have only be described in case reports or small sample size studies. Each technique has its own advantages and disadvantages and unfortunately no randomized control trials or prospective comparative studies between the techniques have been published.

Resection and/or Substitution Techniques

A post-anastomotic aneurysm occurring in a short segment of vein can be treated by resection of the aneurysm and creation of a new anastomosis more proximally. The main advantage of this technique is that an uninvolved segment of vein is immediately available for cannulation.

The resection of an aneurysm and substitution can be performed using either prosthetic or autologous material. The largest study on the resection and substitution technique was published by Georgiadis et al. and included 44 patients with true or false vascular access-related aneurysms (26 in AVF and 18 in AVG) [41]. Most of these patients underwent resection of the aneurysm and interposition with a prosthetic conduit. The primary patency rates of the AVAs were 82% and 57% at 6 and 12 months, respectively. In a study by Pasklinsky et al. of ten patients with AVFAs, seven patients were treated by excision and repair with the great saphenous vein and three patients were treated with excision and repair with prosthetic material [22]. The median follow-up was 19 months, and the primary patency rate at 12 months was 46.7%. Cingoz et al. reported a patency rate of 100% at three years in a group of twenty-eight patients who underwent aneurysm resection and prosthetic graft interposition under local anaesthesia [42]. Recently, Du Bose et al. published a study on 18 patients with AVFA who underwent repair procedures using a tubularized extracellular matrix conduit after AVFA resection [43]. Only five patients underwent a follow-up ultrasound examination; at a mean follow-up time of 6.9 months, two thrombosis events were observed.

The advantage of the aforementioned techniques is the possibility of treating all types of access aneurysms, including those with thrombosis. However these techniques require that the proximal and distal vein segment is free from thrombosis to allow construction of end-to-end or end-to-side anastomoses. Prosthetic conduits have the advantage that they can be cannulated earlier than autogenous grafts. The major disadvantages of the synthetic grafts are the increased risks of thrombosis and infection when compared to autogenous grafts.

Remodelling Techniques

The remodelling technique (partial aneurysmectomy/aneurysmorrhaphy - resection of part of the aneurysmatic sac, reinforced aneurysmorrhaphy - resection of the aneurysmatic and supporting parts of the vein with mesh external prosthesis and plication), utilizes the native vein to preserve the character of the fistula. Aneurysmorrhaphy was originally described in aortic and others aneurysms by Matas in 1903 [44]. Almehmi and Wang treated 36 patients with partial aneurysmectomy [45]. They reported a primary patency rate of 56% at 6 months. Their mean follow-up time was only 7.1 ± 4.8 months. In 2008, Balaz et al.,

described the reinforced aneurysmorrhaphy with polyester mesh tube (Figure 3) [46]. It has been proposed that implantation of an external mesh prosthesis on the surface of the vein to be repaired decreases the venous wall shear stress, thereby decreasing turbulent blood flow, endothelial damage, and mural thrombus formation [47, 48]. This technique was tested by Berard et al. in 33 patients with an assisted primary patency of 93% at 12 months [21]. In 2010 Balaz and Rokosny designed and developed a new surgical instrument, the aneurysmorrhaphy clamp [49], to simplify and support this technique. The largest series assessing this technique in 62 patients was reported by Rokosny et al. [50] and had assisted primary patency rates at 6 and 12 months of 89% and 80%, respectively (the mean follow-up time was 14.66 ± 12.80 months). There are several advantages of this technique: it is possible to treat AVFs with multiple (concomitant) extensive aneurysms, it is well tolerated, it requires minimal hospitalisation and it has a satisfactory cosmetic effect. The main disadvantage is the need for a temporary tunnelled catheter because cannulation of the repaired fistulae has to be interrupted for 4-6 weeks. In patients treated by aneurysmorrhaphy for solitary aneurysm, haemodialysis should be performed by cannulation of the non-dilated part of the vein above the aneurysmorrhaphy segment. Even when the reinforced aneurysmorrhaphy uses an external prosthetic support the infection rate is lower than 5% [21, 50]. An interesting remodelling salvage technique described in a case report by Grauhanet al. consisted of aneurysmorrhaphy followed by the insertion of a highly flexible metal mesh tube into the fistula. Unfortunately, follow data was not reported [51].

Others authors published their experience with aneurysmorrhaphy without external mesh support. Woo et al. performed aneurysmorrhaphy without an external mesh prosthesis in 19 patients with a median follow-up of 23 months (IQR 22 months) [52]. They observed a median primary patency of 14 months (IQR 24 at 12 months). In study by Patel et al. 48 patients underwent open repair with aneurysmorrhaphy [19]. On follow-up (<1 year) no patients experienced AVF thrombosis and secondary angioplasty was performed in 13 patients (27%) to maintain adequate outflow. Hossny reported 14 patients treated by partial aneurysmectomy with reduction venoplasty [53]. The mean follow-up period was 30.4 ± 14.4 months and cumulative patency rates were 85.7% and 64.3% at 12 and 24 months, respectively. Even though the results of the aforementioned remodelling techniques with or without external support are comparable, the effect of external support for maintaining patency is not clear and more comparative studies are needed.

Various others remodelling techniques have been published. Belli et al. published a study on the treatment of 31 patients by excision of the aneurysm/pseudoaneurysm and repair with primary suturing (n = 14), interposition grafting (n = 12) and ligation (n = 5) [54]. They reported a patency rate of 44% at 24 months. Powell et al. recently reported thirty-five patients, who underwent long-segment plication over a 20-Fr plastic tube with or without segmental vein resection, with postoperative functional primary patency 88% at a short-term end point of 30 days [55]. In a study by Sigala et al., 31 patients underwent autologous reconstructions: 5 resections with end-to-end anastomosis and 26 aneurysmorrhaphies. They reported primary patency rates of 81% and 81% and secondary patency rates of 96% and 90% at 1 and 2 years, respectively [56].

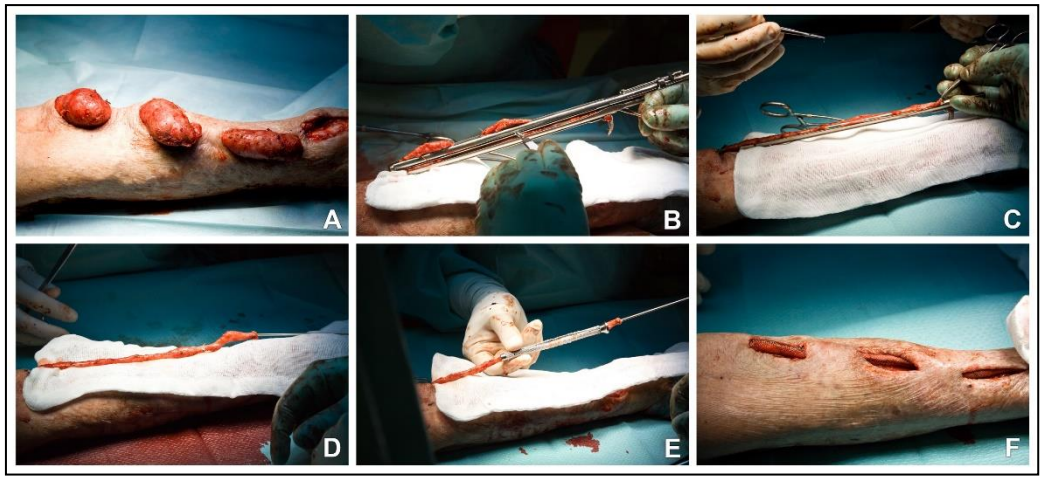

Figure 3. Reinforced aneurysmorrhaphy technique [50]. A – the venous arm of the fistula mobilised up to the nondilated part of the vein, B – resection of aneurysms using BalRok clamp, C – vein wall remaining after aneurysmatic resection sutured by a continuous running suture, D – repaired vein after aneurysmorrhaphy, E – implantation of external mesh prosthesis, F – repaired vein tunnelled subcutaneously and re-anastomosis.

The first study on AVFA resection using staples was published by Hakim et al. in 1997 [57]. Unfortunately, follow up and patency rates were not described. Pierce et al. published a technique of partial resection using staples in 28 diffuse aneurysms in 12 patients [58]. In the mean follow-up period of 29 months one AVF was thrombosed and one AVF was ligated to relieve pain. The remaining AVFs were used for haemodialysis until the patients died (n = 7) or were lost to follow-up (n = 1). Piccolo et al. used aneurysmorrhaphy utilizing a thoracoabdominal stapler in 10 patients and reported primary and primary assisted patency at 6 months (average follow-up period 11 months) to be 80% and 90%, respectively [59]. The largest study for this type of procedure was published by Vo et al., which reported on 40 patients, of whom 38 (95%) underwent successful repair with the staple aneurysmorrhaphy technique. The median follow up period was 20 months and assisted primary patency was 88%, 84%, and 69% at 1, 2 and 3 years, respectively [20].

Endovascular Techniques

There has been a rapid increase in the use of endovascular techniques in vascular surgery and these techniques have been incorporated into the management of vascular access. The first reported successful use of a covered stent to treat AVFA was reported by Allaria et al. in 2002 [60]. Since then Shemesh et al. described the use of stent grafts to treat nine graft access pseudoaneurysms and 11 native vein access aneurysms and pseudoaneurysms, with a functional patency rate of 87% at 12 months with median follow up of 15 (6.3-55.5) months [18]. The advantage of using a stent graft is that it can be performed as an outpatient procedure and allows early venepuncture so that dialysis regimens do not need to be interrupted [61, 62]. Although the patency rate is comparable to the previously described remodelling techniques, stent graft implantations excludes patients with steal syndrome, aneurysms close to the anastomosis and large aneurysms lacking a stent graft sealing zone.

Based upon the available evidence, the stent graft should be considered in patients with type I, II and III aneurysms of Balaz et al. classification. The higher cost of the endovascular treatment of aneurysmatic vascular access remains a concern [5].

Surgical Techniques for High Flow AVFA

As previously mentioned, complications of high flow AVFs are high flow steal syndrome (SS) and high output cardiac failure (HOCF). Treatment options are similar for both complications and include flow-limiting procedures (plication, banding and minimally invasive limited ligation endoluminal-assisted revision (MILLER)), distal revascularization with interval ligation (DRIL), proximalization of arterial inflow (PAI), revascularization using distal inflow (RUDI), transposition of radial artery, proximal radial artery ligation (PRAL) and ligation of the AVF.

Even though there have been numerous studies focused on the treatment of high flow vascular access, only a few of them are focused on aneurysmatic high flow vascular access. Both high flow SS and HOCF can occur with or without presence of aneurysm. This chapter focuses on treatment of AVFA causing high outflow steal syndrome and high output cardiac failure.

In a study by Sigala et al., 31 patients underwent autologous reconstructions: 5 resections with end-to-end anastomosis and 26 aneurysmorrhaphies [56]. In nine patients (29%) with high flow-associated cardiac failure, in followed up period 33 ± 13 months, postoperative decrease in access flow was observed (from 2,356 ± 1,184 mL/min to 1,361 ± 367 mL/min). Hossny reported 14 patients treated by partial aneurysmectomy with reduction venoplasty; high flow AVFA or massive diffuse venous dilatation were indication for treatment in four (29%) patients, unfortunately, the access flow data were not described [53].

Berard et al. proved the effect of aneurysmorrhaphy with external mesh on patients (n = 16) with high flow AVFs (flow rate >1,500 mL/min) [21]. However, in patients with flow >2,500 mL/minute, the effect was not achieved. Accordingly, the authors do not recommend aneurysmorrhaphy for this group of patients. For fistula located in the forearm with flow rates greater than 2,500 mL/min, proximal radial artery ligation and end-to-end anastomosis between the repaired vein and the distal radial artery (if the ulnar artery is patent) is recommended. For upper-arm high-flow AVF, moving the arterial inflow to the forearm artery is recommended. In a study by Rokosny et al., 62 patients with AVFA were treated by aneurysmorrhaphy with external mesh. Symptoms resolution was observed in all patients (n = 3) with steal syndrome [50]. Twenty-four patients had high-flow AVFA. Decreased flow through the AVF was achieved in 23 of these patients (96%); the average flow reduction was 2,197 mL/min (mean follow up period 14.66 ± 12.80 months). Evidence for effectivity of aneurysmorrhaphy with external mesh prosthesis for high flow AVFA has been provided by Wohlfahrt et al. who evaluated the effect of high-flow AVF reduction on heart remodelling on thirty patients with AVF flow $\geqslant$ 1.5 l min^{-1}[35]. Reduction of high flow AVF leads to reverse cardiac remodelling (decreased LV end diastolic diameter and mass, left atrial and right ventricular diameter and pulmonary pressure), but only in patients with elevated CI ($\geqslant$ 3.9 L/min/m^2). We recommend for high flow AVFA aneurysmorrhaphy with anastomosis

relocation to forearm arteries in cases with upper-arm high flow AVFA, and aneurysmorrhaphy with reduction of the anastomosis in forearm high flow AVFA.

Ligation

Ligation should be considered when the previously described salvage technique is unsuccessful or acute bleeding in an unstable patient occurs. Another indication is high flow AVFA in patients who have been successfully treated with a renal transplantation with the expectation of good long-term function.

Conclusion

AVF aneurysm is characterized by an enlargement of all three vessel layers with a diameter of more than 18 mm. Two classification systems for AVFA have been published. Conservative treatment is recommended for asymptomatic aneurysms. The main indications for treatment of symptomatic AVFA are the severity of the clinical presentation, bleeding prevention and low or high flow. The diameter of AVFA and related cosmetic issues are not indications for the treatment. Even though we lack evidence regarding which surgical treatment option is the method of choice, we recommend techniques utilizing the native vein as a first-line options, so that the nature of the AVF is preserved. According to the literature, the best long-term results are achieved by using aneurysmorrhaphy with or without a external support. Stent graft or ligation of AVFA is recommended for urgent treatment in bleeding patients who are at high risk.

Acknowledgment

Thanks to MU Dr. Adam Whitley for grammar and style corrections.

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Aneurysmorrhaphy is an easy technique for arteriovenous fistula salvage

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Abstract: The life-saving procedures for patients in chronic renal failure (CRF) are hemodialysis (HD) or successful kidney transplantation. HD requires a properly placed and functioning vascular access, most often obtained by creating an arteriovenous fistula (AVF). The long-term patency of AVFs is limited, in addition to other factors, by the development of intimal hyperplasia and the process results in venous wall thickening and progressive fistula occlusion. Another problem is limited patency, due to the development of pseudoaneurysm, which is associated with an increased risk of thrombosis, infection and bleeding, difficult cannulation for dialysis, pain and cosmetic defects. Treatment is focused on rapidly progressing pseudoaneurysms, which can predispose to rupture, technical problems during cannulation because of pseudoaneurysm size or a growing intraluminal thrombus. Most of these patients are scheduled for pseudoaneurysm removal and new fistula construction or, occasionally, an endovascular procedure involving stent graft implantation. This paper describes a simple and inexpensive technique of managing an AVF pseudoaneurysm, i.e. aneurysmorrhaphy. To offset the weakening of the venous wall by suture following aneurysmorrhaphy, an external polyethylene terephthalate (PET) prosthesis was implanted in the vein to prevent the development of intimal hyperplasia in the de novo created AVF. (J Vasc Access 2008; 9: 81-4)

Key words: *Arteriovenous, Fistula, Pseudoaneurysm, PET*

INTRODUCTION

The life-saving procedures for patients in chronic renal failure (CRF) are hemodialysis (HD) or successful kidney transplantation. HD requires a properly placed and functioning vascular access, most often obtained by creating an arteriovenous fistula (AVF) (1). Generally, AVF patency depends on a number of factors. In a study of 215 (native and prosthetic) AVFs, Kalman et al reported a primary patency rate as low as 36% at 24 months (2). A role in AVF occlusion in the early post-operative period is primarily played by an inadequate vein diameter, atherosclerosis of the artery, stenosis in the anastomosis, and HD initiation in a yet immature fistula. The long-term patency of AVFs is limited, in addition to other factors (multiple damage to the vessel wall by cannulation in HD), by the development of intimal hyperplasia, also called neointima, a reference to the migration and proliferation of smooth muscle cells induced by an endogenous growth factor via the lamina elastica interna up to the media. The process results in venous wall thickening (3) and progressive fistula occlusion. Another problem associated with AVF, in addition to its limited patency, is the development of pseudoaneurysms. Pseudoaneurysms are associated with an increased risk of thrombosis, infection, bleeding, difficult cannulation for dialysis, pain and, cosmetic defects (4). Pseudoaneurysms are relatively rare occurrence (2-10%) in prosthetic AVFs compared with autovenous AVFs (5). A pseudoaneurysm per se does not necessarily require surgery. Treatment is focused on rapidly progressing pseudoaneurysms, which can predispose to rupture, technical problems during cannulation because of pseudoaneurysm size or a growing intraluminal thrombus (6). Given the limited patency of an AVF, every effort should be made to salvage a pseudoaneurysm-altered fistula, which is no longer suitable for HD. Most of these patients are scheduled for pseudoaneurysm removal and the construction of a new fistula or, occasionally, an endovascular procedure involving stent graft implantation. This paper aims to present our technical experience with AVF aneurysmorrhaphy combined with the implantation of an external porous polyethylene terephthalate (PET) prosthesis to prevent the development of intimal hyperplasia.

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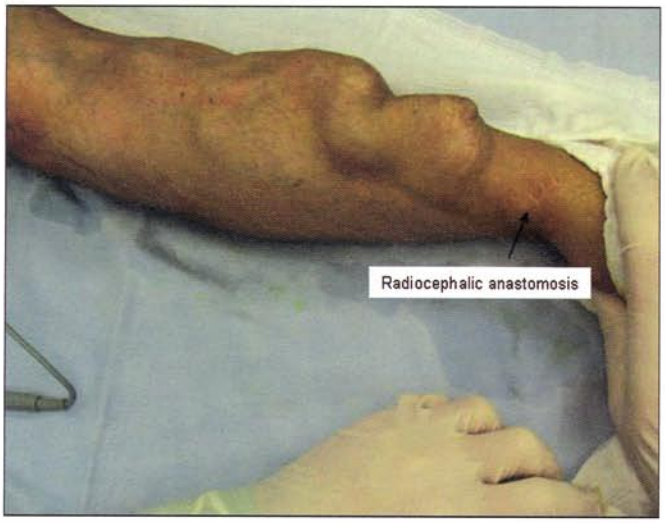

Fig. 1 - ***Pseudoaneurysm of a radiocephalic fistula at 9 years after its construction, arrow indicates the site of anastomosis.***

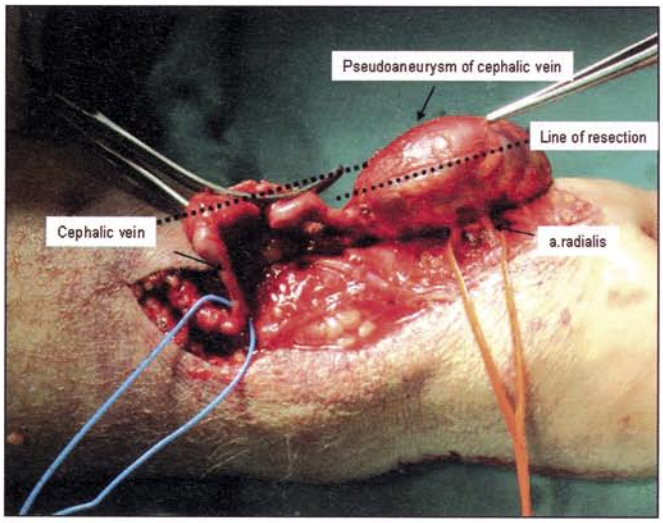

Fig. 2 - ***Pseudoaneurysm trimming.***

MATERIAL AND METHODS

From October 2006 to April 2007, we performed aneurysmorrhaphy of a radiocephalic fistula combined with the implantation of an external porous PET prosthesis in four patients. All four patients (two males, two females), with a mean age of 56 yrs, were in CRF requiring HD.

Technique of aneurysmorrhaphy

The procedure is undertaken under local anesthesia of the interscalenic nervous plexus. With the patient in the supine position, the upper limb is in its maximum abduction and supination. The operating field extends from the axilla down to the elbow. Surgery starts at the site of the arteriovenous anastomosis (Fig. 1). After circumventing it and placing a tourniquet, the whole pseudoaneurysm is mobilized (Fig. 2) up to the non-dilated section of the vein. Special care is given to the nerves running across the operating field. Once the whole pseudoaneurysm has been isolated, we administer a total of 5,000-10,000 IU of heparin and place clamps, first on the supplying artery, then on the non-dilated vein. Immediately above the anastomosis, the fistula is cut apart, leaving behind a patch of part of the pseudoaneurysm, facilitating the construction of a new anastomosis. Next, clamps are gradually placed on the aneurysm sac and after checking its diameter by saline instillation, it is resected and the wall sutured (aneurysmorrhaphy) with continuous suture 6/0 (Fig. 3). The whole section of the vein altered by the aneurysm is managed in this way to obtain the required diameter, which should not be greater than 6 mm. After measuring the diameter of the aneurysmorrhaphy-treated vein, the external porous PET prosthesis (ProVena©, BBraun) is implanted in it. A new anastomosis is created at the site of the original connection (Fig. 4). Heparin is neutralized by an adequate dose of protamine sulfate and, upon checking hemostasis, a Redon drain is placed and the subcutaneous tissue and the skin are closed. In the post-operative period anticoagulation and antiaggregation drugs were not used.

RESULTS

The early post-operative course was uneventful in all patients. On post-operative day 2, one patient experienced bleeding from the resected segment of the aneurysmatic fistula with hematoma formation, which required surgical revision. The external prosthesis was removed due to suspected infection. The ensuing course was uneventful. In all patients, HD was initiated using the modified radiocephalic fistula with implanted external porous PET prosthesis within 4-6 weeks of surgery. No problems with HD were seen in any of the patients.

DISCUSSION

Currently, there are three options to manage symptomatic AVF pseudoaneurysms. First, the pseudoa-

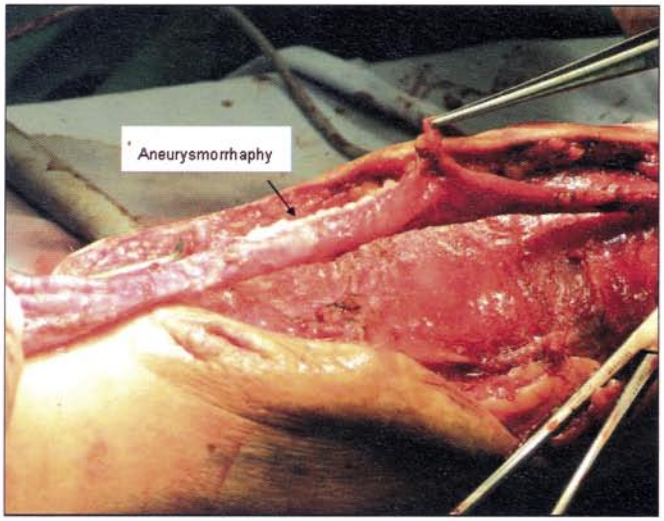

Fig. 3 - *Aneurysmorrhaphy.*

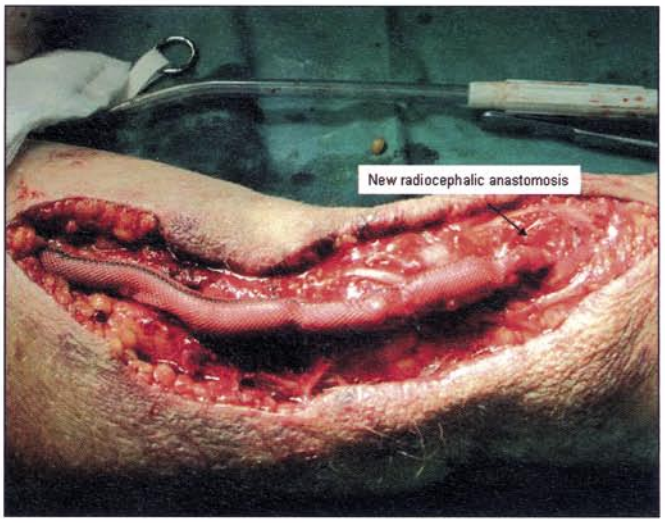

Fig. 4 - *New radiocephalic anastomosis.*

neurysm can be removed while creating a new AVF; a second option is relatively costly - endovascular implantation of stent grafts, and the third one is aneurysmorrhaphy. While experience with the endovascular approach is good, studies reporting the method included small series of patients with short-term follow-up (7-9). As regards AVF aneurysmorrhaphy, the available literature contains almost no relevant information, perhaps because the preferred option in managing a pseudoaneurysm is to eliminate the fistula and create a new one or the endovascular approach. Our paper describes a simple and inexpensive technique of managing an AVF pseudoaneurysm, ie aneurysmorrhaphy, which we performed in four patients. To offset the weakening of the venous wall by suture following aneurysmorrhaphy, an external PET prosthesis was implanted in the vein to prevent the development of intimal hyperplasia in the de novo created AVF. The development mechanism of intimal hyperplasia is because a vein transplanted from an arterial bed undergoes structural alterations due to new hemodynamic conditions (10). Neointimal formation is a complex and multifactorial process in response to the migration of smooth muscle cells from the media to the intima in combination with physical, cellular and humoral factors resulting in endothelial dysfunction (11). The main factors involved in neointimal formation include the quality of the venous graft (valve, branch, varicose lesions and wall abnormality), damage to the vein during its preparation (dissection, stretching, preservation and storage) and changes in hemodynamic circumstances. Increases in blood pressure in the vein entail increased longitudinal and tangential-pulsatile stretch and circular wall deformation (12). These hemodynamic changes have a direct effect on the proliferation of smooth muscle cells, their migration into the intima and the production of endogenous growth factor with endoluminal matrix synthesis eventually resulting in the thickening of the venous wall and the narrowing of its lumen (13). The fact that intimal hyperplasia development is reduced by the use of external prosthetic materials is explained by reduced tangential expansion of the graft wall, decrease in turbulent blood flow and, hence, reduced endothelial damage and mural thrombus formation (14, 15). Barra et al were the first to describe implantation of an external prosthetic mesh on the saphenous vein, in 1986, in four patients with angiographically documented patency at 2 months post-reconstruction (14). Deriu et al reported on the use of an external PTFE prosthesis in 30 patients under vascular peripheral reconstruction. Histological post mortem findings revealed an arterialized venous graft with minimal intimal hyperplasia (16). Implantation of a polyester mesh onto a venous graft with varicose lesions in coronary and infrainguinal vascular reconstruction procedures has resulted in good short-term patency of reconstructed segments. However, data on long-term outcomes are lacking (17-19). A study by Melliere et al reported on a group of six patients, with a half implanted a PTFE mesh on varicose segments of the great saphenous vein and the other half implanted a Dacron mesh on the whole venous graft. No complications were seen during a mean follow-

up of 3 yrs, and all reconstructions were patent (20). In our groups, an external porous PET prosthesis was used in four patients undergoing aneurymorrhaphy of a radiocephalic fistula at the same time. In addition to its wall weakened by previous HD sessions and suture after aneurysmorrhaphy, such a modified AVF is at increased risk of intimal hyperplasia development, providing an opportunity for the formation of a new pseudoaneurysm and accelerated development of intimal hyperplasia on the damaged part of the endothelium. In this indication, external prosthesis implantation is justified in our view. Future enlargement of our group of patients and their longer follow-up will furnish detailed information on the long-term patency of AVF pseudoaneurysms managed as described above.

Conflict of interest statement: None declared.

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První zkušenosti s využitím zevní pórované PTFE protézy v chirurgii arteriovenózních zkratů

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Souhrn

Baláž P., Rokošný S., Klein D., Trubač R., Adamec M.: První zkušenosti s využitím zevní pórované PTFE protézy v chirurgii arteriovenózních zkratů

Autoři prezentují první zkušenosti s implantací zevní pórované PTFE protézy při transpozici basilické žíly u brachiobasilické píštěle u 5 pacientů a při ošetření pseudoaneuryzmatu radiocefalické píštěle u 4 pacientů v období 10/2006 – 4/2007. Implantace zevní pórované PTFE protézy při transpozici žil k vytvoření AVF má význam v prevenci vzniku pseudoaneuryzmatu a současně v prevenci vzniku intimální hyperplazie. Implantace zevní protézy je indikována při aneurysmorrhafii, kde je stěna žíly po sutuře oslabená a vzniká tak predispozice ke vzniku nového pseudoaneuryzmatu.

Klíčová slova: AVF – transpozice – aneuryzmorrhafie – PTFE

Summary

Baláž P., Rokošný S., Klein D., Trubač R., Adamec M.: First Experience with PTFE Mesh Prothesis in Surgery of Arteriovenous Access

The authors present their initial experience with implantation of external porous PTFE prosthesis in transpositioning of the basilic vein in brachiocephalic fistules in 5 patients and in the management of radiocephalic fistules in 4 subjects during, operated from October 2006 to April 2007. Implantation of the external porous PTFE prosthesis in venous transpositions to form AVFs is aimed at prevention of pseudoaneurysms formation , as well as at prevention of development of intimal hyperplasias. The external prosthesis implantation is indicated in aneurysmoraphies, where the venous wall is weakened as a result of its suturing, which makes it predisposed for development of a new pseudoaneurysm.

Key words: AVF – transposition – aneurysmoraphy – PTFE

Rozhl. Chir., 2007, roč. 86, č. 9, s. 475–479.

ÚVOD

Pro pacienty v chronickém renálním selhání je život zachraňující hemodialýza nebo úspěšná transplantace ledviny. Pro hemodializační léčbu je nezbytný správně umístněný a funkční cévní přístup, který se nejčastěji získává vytvořením arteriovenózních spojek (AVF). Strategie vytváření AVF je všeobecně známá, jako první volba je zakládání nativních AVF a až poté se přistupuje k zakládání protetických zkratů. Jako jednou z možností vytvoření nativního arteriovenózního zkratu jsou operace spojené s transpozicí žil k vytvoření tepenně-žilního spojení. V této indikaci se často využívá spojení transponované basilické žíly s brachiální tepnou, popsaná Dagherem již v roce 1976 [1]. Výhodou basilické žíly je její dobrá kvalita, protože svým subfasciálním uložením je chráněná před venepunkcemi a kanylacemi. Další možností vytvoření AVF je použít u indikovaných pacientů k vytvoření zkratu existující, pseudoaneuryzmaticky změněný zkrat, který je již nevhodný k aplikaci hemodialýzy. Tato technicky náročná operace spočívá v resekci vaku aneuryzmaticky změněné žíly, úpravě jejího průměru a konstrukce nové anastomózy s tepnou.

Obecně průchodnost AVF závisí na mnoha faktorech a podle studie Kallmana na 215 AVF (nativních i protetických) je primární průchodnost za 24 měsíců jen 36 % [2]. Při uzávěru AVF v brzkém období hraje roli především nevhodný průměr použité žíly, ateroskleróza tepny, stenóza v anastomóze a zahájení hemodialýzy na ještě nematurovanou spojku. Dalšími faktory včasného uzávěru jsou koagulační poruchy a celkové onemocnění pacienta. Tyto faktory je možné eliminovat výběrem správné strategie operace a šetrnou technikou operace. Dlouhodobé užívání antiagregační a antikoagulační terapie je diskutabilní. Dlouhodobou průchodnost arteriovenózních píštělí limituje, kromě jiných faktorů (opakované poškozování cévní stěny kanylacemi při hemodialýze), vznik intimální hyperplazie nebo taky označované jako neointima, což zahrnuje migraci a proliferaci hladkých svalových buněk na podnět endogenně produkovaného růstového faktoru přes lamina elastica interna až do

medie. Tento proces vede ke ztluštění žilní stěny [3]. Vznik intimální hyperplazie je komplexní multifaktoriální proces, který není ještě dokonale prostudován [4]. Je proto nutné volit vhodnou strategii operace a vynaložit maximální úsilí k záchraně funkce arteriovenózních píštělí. Jedním z příkladů nepoužitelné AVF je mohutné pseudoaneuryzma, které pro své rozměry a křehkou stěnu již nedovoluje aplikaci hemodialýzy. Pseudoaneuryzma má i další atributy, které dělají obtíže pacientovi. Bolest, strach z poranění a v neposlední řadě i neestetický dojem. U většiny těchto pacientů se setkáváme s indikací k odstranění pseudoaneuryzmatu a konstrukce nové píštěle.

Jednou z možností prevence vzniku intimální hyperplazie v žilním štěpu je ovlivnění hemodynamiky, které je žilní stěna v arteriálním řečišti vystavena [4]. Na trhu je dostupná zevní pórovaná PTFE protéza (ProVena©, fy.B.Braun), která byla vyvinuta k použití na periferní cévní rekonstrukce k ochraně infrainguinálních žilních bypasů. Protéza působí proti tangenciálnímu rozpínání žíly a tím snižuje turbulenci krevního toku, což snižuje tvorbu intimální hyperplazie.

Cílem tohoto sdělení je prezentovat vlastní zkušenosti autorů s implantací zevní pórované PTFE protézy při transpozici basilické žíly u brachiobasilické píštele a při ošetření pseudoaneuryzmatu radiocefalické píštěle.

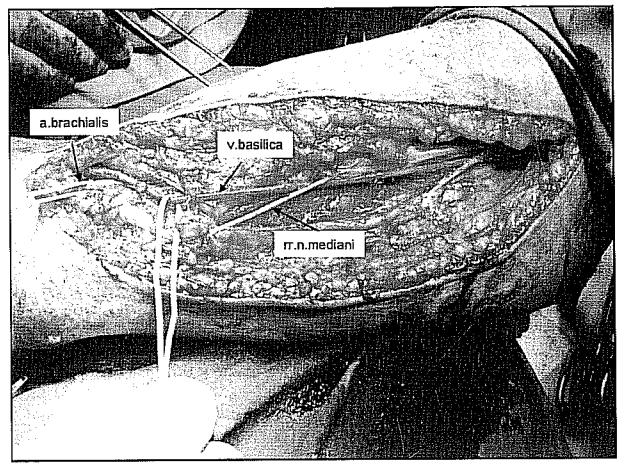
MATERIÁL A METODY

V období 10/2006 – 4/2007 jsme provedli transpozici basilické žíly s implantací zevní pórované protézy u 5 pacientů a u 4 pacientů po resekci pseudoaneuryzmatu radiocefalické píštěle. Všichni pacienti s průměrným věkem 56 let, 5 mužů, 4 ženy, měli chronické renální selhání s nutností hemodializační léčby.

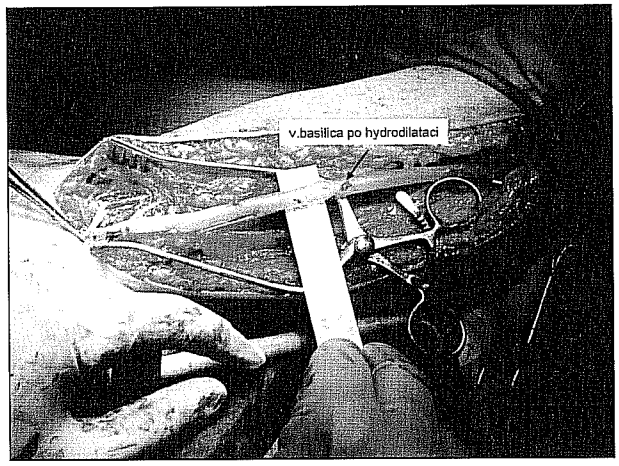
Technika transpozice basilické žíly

Podstatou operace je preparace a uvolnění basilické žíly z subfasciálního prostoru s vytvořením arteficiálního subkutánního tunelu, kde se žíla transponuje a end-to-side anastomóza s brachiální tepnou.

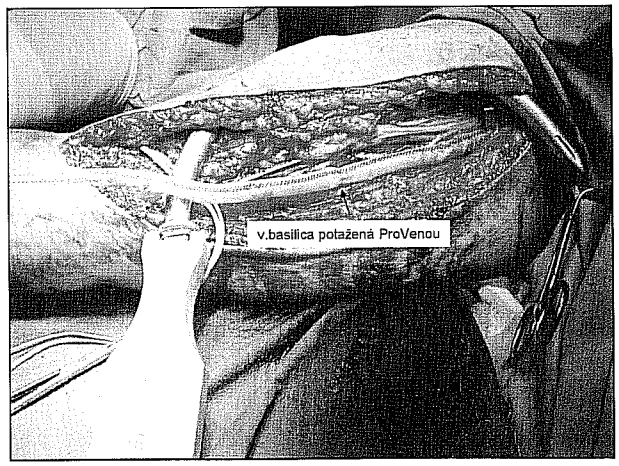
Operace je většinou vedena v regionální anestezii interscalenického nervového plexu. Při poloze pacienta na zádech je horní končetina v maximálni abdukci a supinaci. Operační pole je tvořeno prostorem od axily až ke kubitě. Z obloukovitého řezu nad mediálním epikondylem humeru preparujeme basilickou žílu a brachiální tepnu. Prodloužením řezu až do axily izolujeme basilickou žílu až k soutoku s brachiální žílou, s ohledem na nervus cutaneus brachii medialis, který probíhá v těsném sousedství s basilickou žílou (Obr. 1). Po izolaci celé basilické žíly podvazujeme pečlivě její odstupy. Následuje její přerušení distálně a šetrná dilatace instilací fyziologického roztoku (Obr. 2). Po změření průměru dilatované žíly implantujeme zevní pórovanou protézu (Obr. 3). Vytvořeným podkožním tunelem takto připravenou žílu transponujeme do podkoží až k místu anastomózy s brachiální tepnou (Obr. 4). Anastomózu typu end-to-side konstruujeme po 4–5mm arteriotomii 6/0 monofilamentním vláknem. Po kontrole hemostázy a funkčnosti píštěle zavádíme Redonův drén a po zašití fascie po odběru žíly uzavíráme operační ránu.



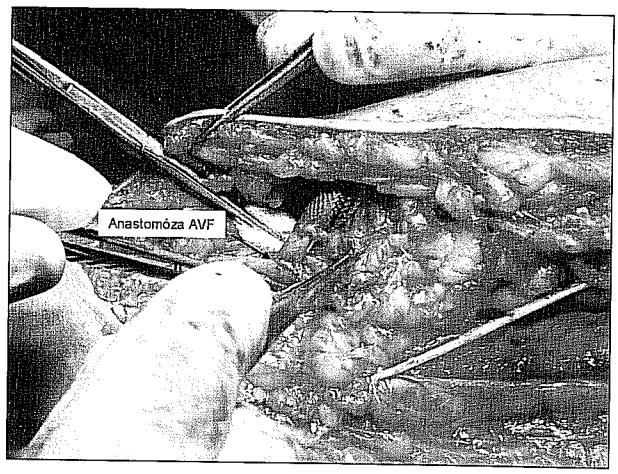
Obr. 1. Vypreparovaná vena basilica
Fig. 1. The preparated vena basilica



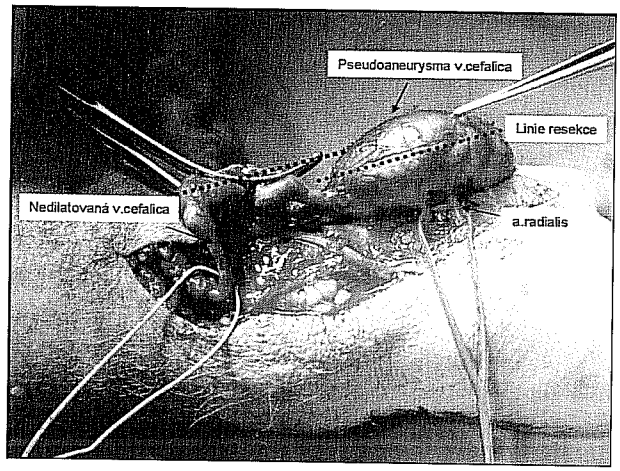
Obr. 2. Hydrodilatace vena basilica
Fig. 2. Hydrodilation of the vena basilica



Obr. 3. Aplikace zevní protézy na basilickou žílu
Fig. 3. Application of the external prosthesis to the basilic vein



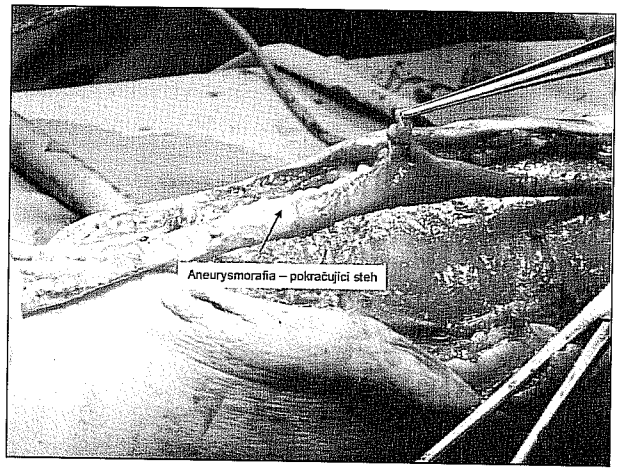
Obr. 4. Anastomóza vena basilica s arteria brachialis
Fig. 4. Anastomosis between the vena basilica and arteria brachialis



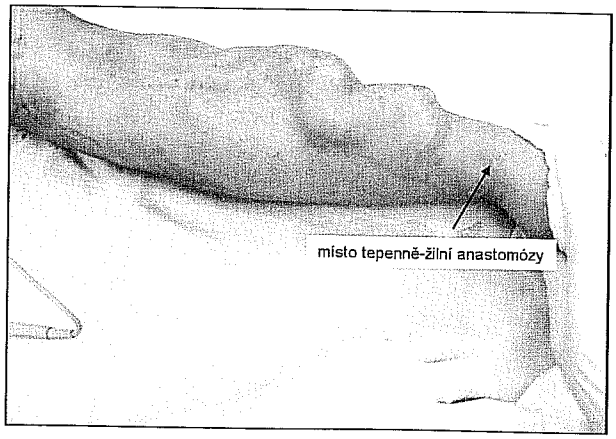
Obr. 6. Preparace pseudoaneuryzmatu
Fig. 6. Preparation of the pseudoaneurysm

Technika aneurysmorrhafie

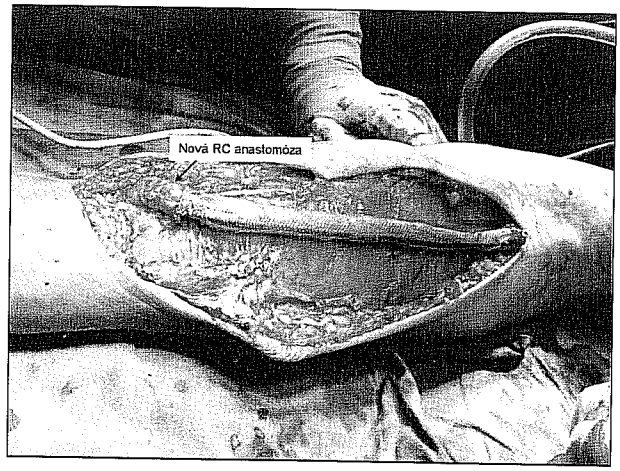
Operaci provádíme v regionální anestezii intreskalenického nervového plexu. Poloha pacienta je stejná jak při transpozici vena basilica. Operaci zahájíme preparací v místě arteriovenózní anastomózy (Obr. 5). Po obejití a naložení turniketu vypreparujeme celou pseudovýduť (Obr. 6) až do místa nedilatované části žíly. Při preparaci věnujeme pozornost probíhajícím nervům. Po izolaci celého pseudoaneuryzmatu podáme celkově 5000–10000 UI Heparinu a naložíme nejprve svorku na zásobující tepnu, poté na nedilatovanou žílu. Těsně nad anastomózou píštěl přerušíme, aby nám zůstal terč z části pseudovýdutě, který nám ulehčí konstrukci nové anastomózy. Postupně nakládáme svorky na vak vydutě a po kontrole průměru instilací fyziologického roztoku, provádíme její resekci a suturu stěny – aneurysmorrhafii pokračujícím stehem 6/0 (Obr. 7). Takto ošetříme celou aneuryzmaticky změněnou žílu na požadovaný průměr, který by neměl přesáhnout 6mm. Na takto upravenou žílu „navlékneme" zevní pórovanou protézu postupem uvedeným při transpozici basilické žíly. Konstruujeme



Obr. 7. Aneurysmorrhafia
Fig. 7. Aneurysmorrhaphy



Obr. 5. Pseudoaneuryzma radiocefalické píštěle 9 let od založení, šipka znázorňuje místo anastomózy
Fig. 5. A pseudoaneurysm of a radiocephalic fistule 9 years following its completion, the anastomosis is marked by an arrow



Obr. 8. Nová radiocefalická anastomóza
Fig. 8. New radiocephalic anastomosis

novou anastomózu v místě původního spojení. Neutralizujeme heparin adekvátní dávkou protaminsulfátu a po kontrole hemostázy zavedeme Redonův drén a uzavíráme podkoží a kůži (Obr. 8).

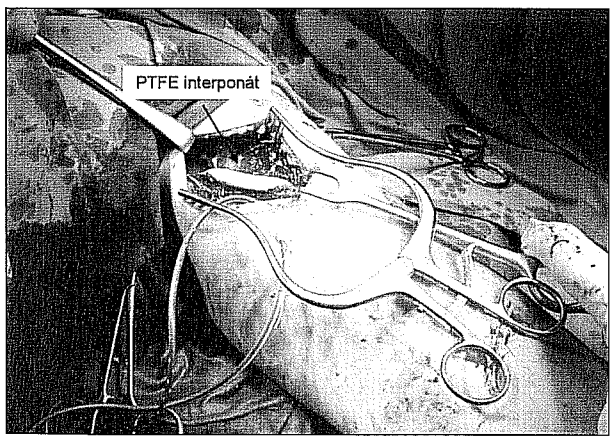
VÝSLEDKY

Včasný pooperační průběh byl bez komplikací u 8 z 9 pacientů. U jednoho pacienta nastalo druhý pooperační den krvácení z resekované části aneuryzmatické píštěle s hematomem, které si vyžádalo chirurgickou revizi. Vzhledem k podezření na infekci byla odstraněna zevní protéza. Další průběh byl již bez komplikací.

Pozdní komplikací (po 3 měsících) byla u jednoho pacienta stenóza v odstupu transponované bazilické žíly v soutoku s brachiální žílou, způsobená zalomením v místě přechodu do podkoží. Byla indikovaná fistulografie s pokusem o angioplastiku, kde při dilataci řezacím balonkovým katétrem došlo k perforaci žilní stěny. Tato komplikace si vyžádala urgentní chirurgickou revizi s náhradou poškozené žilní stěny protetickým PTFE interpozitem (Obr. 9). U druhého pacienta po transpozici basilické žíly jsme pozorovali v průběhu 2 měsíců parestezie v oblasti mediální strany paže, způsobené poškozením větve nervus cutaneus brachii medialis, obtíže spontánně vymizely za 6 týdnů.

U všech operovaných pacientů byla zahájena hemodialyzační léčba vytvořenou AVF s zevní pórovanou PTFE protézou v období 4–6 týdnů od operace.

U žádného pacienta nebyly zaznamenány problémy s hemodialýzou.



Obr. 9. PTFE protézou nahrazená část perforované basilické žíly
Fig. 9. A PTFE prosthesis replacing a section of the perforated basilic vein

DISKUSE

S implantací zevní pórované PTFE protézy při transpozici žil a aneurysmorhafií pro vytvoření arteriovenózního zkratu nejsou v literatuře dostupné žádné informace. Obecně se před transpozičními operacemi upřednostňují protetické arteriovenózní píštěle, pro menší náročnost operace a kratší operační čas.

Při řešení pseuaneuryzmatu se spíše indikuje zrušení zkratu s vytvoření nové píštěle.

Jedním z důvodů uzávěru cévních rekonstrukcí je vznik intimální hyperplazie. Žíla, která je chirurgicky přenesena do arteriálního řečiště, prochází strukturálními změnami vlivem nových hemodynamických poměrů [5]. Etiologie vzniku neointimy je komplexní a multifaktoriální proces jako odpověď na migraci hladko svalových buněk z medie do intimy v kombinací s fyzikálními, celulárními a humorálními faktory, které vedou k dysfunkci endoteliální regulace [6]. Hlavními faktory podílející se na vzniku neointimy jsou kvalita žilního štěpu (chlopně, větve, varikózní změny a abnormalita stěny), poškození žíly při preparaci (disekce, natažení, uchovávaní) a změny hemodynamických poměrů. Zvýšení tlaku krve v žíle vede k zvýšení longitudinálního a tangenciálního-pulzativního napětí a cirkulárním deformacím stěny [7]. Tyto hemodynamické změny mají přímý vliv na proliferaci hladko svalových buněk, jejich migraci do intimy a produkci endogenního růstového faktoru se syntézou endoluminálního matrix, což vede ke ztluštění žilní stěny a zúžení jejího lumen [8]. Minimalizace poškození žilní stěny během operace šetrnou operační technikou redukuje zánětlivou odpověď poškozeného endotelu. Avšak, výsledky se snížením míry vzniku intimální hyperplazie nejsou jednoznačné [9]. Taktéž antilipidová farmakologická léčba je neúspěšná v prevenci dlouhodobého uzávěru žilních štěpů [10]. Na druhé straně deriváty kyseliny acetylsalicylové zlepšují dlouhodobou průchodnost femoro-popliteálních bypasů [11]. Ovlivnění vzniku intimální hyperplazie použitím zevních protetických materiálů se vysvětluje redukcí tangenciálního rozpínání stěny štěpu, snížením turbulentního toku krve a tím snížení poškození endotelu a vzniku nástěnné trombózy [12, 13]. Prvním, který publikoval implantaci zevní protetické síťky na venu safenu byl Barra v roce 1986 u čtyřech pacientů s angiograficky potvrzenou průchodností rekonstrukce dva měsíce [12]. Deriu a kolektiv popsali použití zevní PTFE protézy u třiceti pacientů při cévní periferní rekonstrukci. Histologické post mortem nálezy ukázaly arterializovaný žilní štěp s minimální intimální hyperplazií [14]. Implantace polyesterové síťky na varikózně změněný žilní štěp v koronárních a infrainguinálních cévních rekonstrukcích ukázala dobrou krátkodobou průchodnost rekonstrukcí. Údaje o dlouhodobých výsledcích však chybí [15, 16, 17]. V práci Melliera byl popsán soubor šesti pacientů, kde u poloviny byla implantována PTFE síťka na varikózní úseky velké safény a u druhé poloviny byla implantována dakronová síťka na celý žilní štěp. V průměrném follow up tři roky nebyly zaznamenány žádné komplikace a všechny rekonstrukce byly průchodné [18].

V našem souboru jsme zevní pórovanou PTFE protézu použili u dvou rozdílných skupin pacientů. V první skupině jsme implantovali protézu při transpozici vena basilica k vytvoření brachiobasilické píštele a druhou skupinu tvořili pacienti s pseudoaneuryzmatem radiocefalické píštele, kdy bylo původně indikováno její zrušení a založení nové arteriovenózní spojky. Při transpozičních operacích u pacientů, kde se předpokládá dlouhodobé využívání píštěle a není indikovaná transplantace ledviny pro přítomnost vážných komorbidit, je potřebné vynaložit maximální úsilí o prodloužení průchodnosti vytvořené píštěle. Implantace zevní protézy při transpozici žil k vytvoření AVF má význam v prevenci vzniku pseudoaneuryzmatu a současně v prevenci vzniku intimální hyperplazie. Po aneurysmorrhafii je stěna po sutuře oslabená a poškozená. Tyto faktory tak dávají možnost vzniku nového pseudoaneuryzmatu a urychlují vznik intimální hyperplazie na poškozené části endotelu. V této indikaci je implantace zevní protézy opodstatněné. V budoucnosti nám další sledovaní pacientů přinese podrobné informace o dlouhodobé průchodnosti arteriovenózních píštělí s implantovanou zevní pórovanou PTFE protézou.

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