Factors influencing the recurrence of arterial involvement after surgical repair in Behçet disease

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ARTICLE HIGHLIGHTS

Type of Research: single center retrospective study

Key Findings: Twenty-three patients with BD, had aortic and peripheral arterial repair between May 1996 and September 2015. Twenty-four recurrences were noted and forty-seven surgical procedures were performed. Mean follow-up was 8.4±7.5 years. Initial arterial lesions were aneurysms and thrombosis in 85% and 15% of cases, respectively. Recurrence rate was 51%.

Preoperative medical treatments, including colchicine, steroids or immunosuppressants, significantly decreased recurrence rate: 28% (7/25) *versus* 75% (15/20) in untreated patients (P = 0.002). When anastomoses were protected using a prosthetic sleeving technique, the recurrence rate was threefold lower (P = 0.08).

Take home Message: Vascular Behçet's disease is responsible for a high rate of recurrence after surgical repair. Perioperative immunosuppressants are essential to reduce this risk. The additional surgical technique consisting in sleeving anastomosis may help to reduce pseudoaneurysm recurrences occurring at the same site in 92% of cases.

Table of Contents Summary

Recurrence after surgical repair occurred in 51% of cases in this retrospective study of 23 patients with non-pulmonary arterial involvement of BD. Immunosuppressive treatment but also mechanical sleeving of the anastomosis decrease recurrence rates.

Abstract

Introduction: Arterial involvement in Behçet's disease (BD) is rare and its surgical management is a major concern because of its high recurrence rate. This study evaluated the influence of the surgical technique, device, and immunosuppressive treatment used on the postoperative recurrence in patients with non-pulmonary arterial BD.

Methods: Single center retrospective study conducted in 23 patients meeting the International Study Group of BD criteria, who underwent surgery for arterial involvement between May 1996 and September 2015. Recurrence was defined as the occurrence of arterial aneurysm or thrombosis during follow-up. Perioperative medical treatment and surgical technique used were reported.

Results: Forty-seven surgical procedures were performed in 23 patients. Mean follow-up was 8.4±7.5 years. Initial arterial lesions were aneurysms and thrombosis in 85% and 15% of cases, respectively. Arterial lesions were aortic and peripheral in 48% and 52% of cases. Recurrence rate was 51%. Recurrences occurred within less than one year in 24% of cases and at the same anatomical site in 92% of cases. Among the 24 recurrences, 17 were false aneurysms, 6 were thrombosis and one was a true aneurysm in a different arterial site. To treat the arterial lesion, direct anastomosis was performed in 6 cases, bypass using the saphenous vein, graft or allograft was performed in 6, 27 and 5 cases, respectively, and stentgraft was used in 3 cases. Vascular lesions involved the aorta in 19 cases and a peripheral artery in 28 cases.

Preoperative medical treatments, including colchicine, steroids or immunosuppressants, significantly decreased recurrence rate: 28% (7/25) *versus* 75% (15/20) in untreated patients (P = 0.002). The recurrence rate was 42.5% (17/40) in patients treated postoperatively *versus* 80% (4/5) in untreated patients. The nature of the device used (vein, prosthetic graft, allograft, stent graft or direct anastomosis) did not change the risk of recurrence. When anastomoses

were protected using the prosthetic sleeving technique, the recurrence rate was three times lower (P = 0.08).

Conclusion: Relapse is a main concern after surgical repair of arterial BD. This study suggests the need for targeted perioperative medical management to reduce the risk of arterial recurrence in BD patients. To this end, a multidisciplinary approach is mandatory.

The use of sleeve anastomosis is associated with a numerically lower risk of recurrence. However, further studies are needed to confirm this efficacy.

Key words: Vascular Behçet's disease, aneurysm, recurrence, sleeve anastomosis.

Conflict of interest: None

Introduction

Behçet's disease (BD) is a chronic, relapsing, multisystemic disorder characterized by mucocutaneous, ocular, vascular and central nervous system manifestations[1, 2]. The pathogenesis of the disease remains unknown, although a genetic predisposition, environmental factors, and immunological abnormalities have been reported[3, 4]. Vasculitis is thought to underlie the clinical manifestations of BD and is distinguishable because both arteries and veins of all sizes are involved. Arterial complications are less common than venous lesions in BD, and occur in 1-14% of patients[5-8]. Vascular BD (VBD) patients are at risk of multiple vessel-related complications resulting in an increased risk of mortality. Indeed, the 20-year survival rate decreases from 89 to 73% in case of arterial disease[9]. In a large cohort of 817 BD patients, Saadoun et al.[8] have shown an overall mortality rate of 5% after a median follow-up of 7.7 years. In this series, the incidence of arterial involvement was 3 times higher in patients who died. Unlike venous manifestations[10-15], arterial involvement in BD is rare and a few publications have reported its specific treatment. Vascular surgery is challenging in BD patients and the mortality rate is high[16], mainly due to anastomotic aneurysm relapses and graft thrombosis.

There is currently no consensual technique for the surgical management of these patients. The vascular substitutes that can be used include prosthetic materials, venous autografts, arterial allografts or stent grafts[9]. The main concern in these patients, apart from bypass thrombosis, is the formation of anastomotic pseudoaneurysms in the short term, requiring iterative interventions that may be life-threatening in case of rupture.

The aim of this study was to retrospectively identify the factors influencing the postoperative recurrence of arterial lesions in BD patients with non-pulmonary arterial involvement.

Patients and methods

Population

It was a single center retrospective study conducted in 23 BD patients meeting the international criteria for BD[17] who consulted the Departments of vascular surgery and internal medicine of the Pitié-Salpêtrière Hospital, Paris, France between May 1996 and September 2015.

Associated clinical signs were genital and oral ulcerations, uveitis, folliculitis, arthralgia, and fever. Other aneurysmal locations, a history of deep vein thrombosis and cardiovascular risk factors were identified. Pre- and post-operative medical treatments were recorded. Patients with BD requiring arterial repair in our department were systematically included in the study whether it was a recurrence or a primary surgery. In case of previous arterial repair in another center, the first surgical repair in our department was considered a recurrence. Arterial lesions were defined by the presence of aortic or peripheral aneurysm, pseudoaneurysm or arterial thrombosis. The presence of a potential triggering trauma was also investigated for each arterial lesion. Patients who did not require surgery or with pulmonary artery aneurysms were excluded from the analysis. The indications for surgery were: symptomatic arterial thrombosis; aortic aneurysm greater than 5 cm in diameter or growing by more than 5 mm in 6 months, or becoming symptomatic; pseudoaneurysm of more than 2 cm in diameter or growing. Emergency management was limited to ruptured aneurysms or patients with acute ischemia. The radiological diagnosis of aneurysm or pseudoaneurysm was based on arterial Doppler ultrasound combined with computed tomography (CT)-scan. The surgical technique and the material used (prosthetic graft, saphenous autograft, arterial allograft, or stent) were analyzed according to the different anatomical locations. Bypass anastomosis was performed as usual. The choice of the technique used was left to the referee surgeon's discretion. In some cases, a sleeving protection was used, consisting in locating a short prosthetic graft segment around the vascular anastomosis (figures 1 and 2) to reinforce it and to prevent secondary

pseudoaneurysm formation. This technique was used when the diagnosis of VBD was confirmed or strongly suspected. In these cases, a sleeve protection was used on each end-to-end anastomosis remote from a bifurcation. For large bypasses (diameter >8 mm), the same graft segment is used for sleeving. For ≤8mm bypasses, a larger (+1mm) segment than the bypass graft is required to avoid stenosis.

The postoperative follow-up was based on clinical examination and ultrasound or CT-scan. The primary patency rate was calculated.

A recurrence was defined as the reappearance of aneurysm or pseudoaneurysm at the operated site or in another location, or by the occurrence of bypass thrombosis.

Early recurrence was defined as the occurrence of arterial aneurysm within less than 1 year, confirmed by arterial Doppler ultrasound or CT-scan. Global doppler ultrasound was systematically performed 6 months after surgery and yearly thereafter during the follow-up. In case of thoracic aortic repair, a CT-scan was performed at the same timepoints. Recurrence at the same arterial site and recurrence at a new site were differentiated. The follow-up was performed by the surgical department and by the referent BD medical department located in the same hospital.

The number of recurrences was compared according to the nature of the implanted arterial substitute: synthetic graft, venous autograft, arterial allograft, or stent. The effect of sleeve anastomosis on recurrences was assessed. The recurrence rate in patients receiving dedicated medical treatment for BD was also compared to the recurrence rate in untreated patients, including those who could have benefited from a sleeving or not. Steroids and immunosuppressive treatment were systematically prescribed prior to surgery in BD patients from our institution. However, in some cases, no immunosuppressive treatment was given when patients where referred from other centers or when the diagnosis of BD had not been confirmed prior to surgery.

Ethical issues

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The study protocol was assessed by the institutional review board of the *Hôpital Universitaire Pitié-Salpêtrière*. Patients were informed that their clinical data were likely to be collected, but in accordance with the French law, since this was an observational study involving only routine clinical practices and therefore with no risk for patients, no informed consent was needed.

Statistical analysis

Statistical analyses were carried out using SAS 9.4 software. Quantitative data with normal distribution are expressed as the mean ± standard deviation and quantitative data with non-normal distribution as the median (interquartile). The recurrence rate according to the effect of the anastomotic sleeve technique was assessed using the Kaplan-Meier method. The Fischer's exact test was used to study the effect of preoperative and postoperative treatments on the occurrence of recurrences (thrombosis, false aneurysm). A P-value less than 0.05 was considered statistically significant.

Results

Population

Twenty-three BD patients with arterial involvement were included in our study. A total of 47 procedures were performed for arterial lesion, with a mean number of 2.4 ± 0.6 procedures per patient in the 17 patients who experienced recurrence. Except for 7 initial interventions performed in another hospital before the diagnosis of BD, all interventions were performed in

our department, including after relapses. Patient demographics are presented in Table I. At the time of arterial lesions, the main active clinical sign of BD was oral and genital ulcerations in 61% of cases. Peripheral locations were more common than aortic ones (Table II).

Among patients with peripheral aneurysms, the femoro-popliteal location (48%) was the most common. Among all patients, the first arterial involvement was fusiform aneurysm (n=10), pseudoaneurysm (n=12), or arterial thrombosis (n=1). During the follow-up, including relapses, the treated lesions were pseudoaneurysms in 29 procedures (62%), fusiform aneurysms in 11 procedures (23%) and arterial thrombosis in 7 procedures (15%). The lesions were bilateral in 2 patients (4%): one patient had bilateral iliac thrombosis and one patient had spontaneous bilateral femoral pseudoaneurysms. Arterial puncture resulted in pseudoaneurysm in 2 cases (4%). Emergency management for ruptured aortic pseudoaneurysm below the renal arteries was needed in two cases (4%).

Surgical technique

Among the 47 procedures, 27 prosthetic grafts (57%), 6 venous autologous grafts (13%), 5 cryopreserved allografts (11%) and 3 stent grafts (6%) were used (Table III). Prosthetic grafts were polyethylene terephthalate (PET) in all cases except one. In this case, graft made with polytetrafluoroethylene (PTFE) was used. All anastomoses were performed using polypropylene suture thread. Stent grafts used were Valiant thoracic endograft (Medtronic, Santa Rosa, CA, USA) in one case and covered stents in two cases (fig 3) for peripheral aneurysms. In 6 cases, reconstruction did not require any material (13%) because short resection with direct end-to-end anastomosis could be performed. The vascular substitutes used, depending on the lesion location, are shown in Table III. A total of 95 anastomoses were performed during the 47 procedures. The sleeving technique was used for 25 anastomoses (corresponding to 13 bypass procedures): 23 (92%) were graft-to-artery

anastomosis (8 aortic, 3 iliac, 11 femoral, and 1 popliteal) and 2 (8%) were venous-to-femoral artery anastomosis.

The mean follow-up duration was 8.4 ± 7.5 years. The postoperative mortality rate was 2%. One patient died 1 month after surgery. This patient underwent aortic stent graft in zone 0 with supra-aortic trunk debranching for false aneurysm of the aortic arch. He experienced a septic rupture of the brachiocephalic trunk anastomosis due to *Staphylococcus aureus* graft infection. The postoperative morbidity rate was 8% (4/47). Two patients experienced hematoma at the surgical site, one patient had acute renal failure without dialysis after aortic surgery, and one patient had acute lower limb ischemia due to embolization after treatment of abdominal aortic aneurysm.

The 5-year primary and secondary patency rates were 94 and 100%, respectively.

All patients received antiplatelet therapy (160 mg of acetylsalicylic acid) after bypass surgery regardless of the substitute used. In case of thrombosis, anticoagulant treatment (vitamin K antagonist) was initiated instead of antiplatelet therapy.

Recurrence after vascular repair

A total of 24 recurrences were observed in 17 patients, corresponding to a recurrence rate of 51%. Eleven patients (48%) had 1 recurrence, 5 patients (22%) had 2 recurrences and 1 patient (4%) had 3 recurrences. In 22 cases (92%), the same arterial anatomical site was involved. Only two patients experienced a recurrence in a different site: one patient had contralateral common femoral artery pseudoaneurysm and one had aortic dilation above a previous infra-renal aortic repair.

Lesions recurred as anastomotic pseudoaneurysm in 71% of cases (17/24), bypass thrombosis in 25% of cases (6/24) and aortic fusiform aneurysm above previous infra-renal aortic aneurysm repair in 4% of cases (1/24). Graft thrombosis occurred in three patients (femoro-

femoral bypass in two cases and aorto-aortic graft in one case). Graft thrombosis recurred one, two and three times respectively in these three patients.

The mean time to recurrence for the overall population was 65 ± 68 months. Among the 24 recurrences, 7 (24%) occurred within one year. In the 16 cases that relapsed after one year, the mean time to recurrence was 79.6 ± 59 months. In this group, the median time between the first arterial repair and the first recurrence was 45 months (1-232) and it was 18 months (6-143) between the second intervention and the second relapse. In one patient, the time between the third intervention and the third relapse was 20 years. Recurrences according to the time are presented in Figure 3.

Anastomotic pseudoaneurysm occurred within the first year in 41% of cases (7/17).

The nature of the recurrence observed according to the type of arterial repair is shown in Table IV. The differences highlighted were not statistically significant due to the small size of the sample.

In 45 out of the 47 procedures performed, the use of pre- or postoperative immunosuppressive treatment was known. Medical treatment included colchicine, steroids or immunosuppressants. Patients received medical treatment preoperatively in 55% of cases (25/45), postoperatively in 89% of cases (40/45) and both pre- and postoperatively in 51% of cases (23/45). No medical treatment was given in 11% (5/45) of cases. Perioperative medical treatments are detailed in Table V.

The effect of preoperative immunosuppressive treatment on the recurrence rate showed that 28% of procedures (7/25) were followed by a recurrence in treated patients compared to 75% (15/20) in untreated patients (OR: 7.31; 95% CI (1.73; 36.81)) (P = 0.002).

The effect of postoperative immunosuppressive treatment was also assessed. Forty-two percent of patients who received postoperative treatment (17/40) experienced a recurrence *versus* 80% of untreated patients (4/5) (OR: 5.22; 95% CI (0.46; 277.32)) (P = 0.16).

All patients who did not receive any medication before or after surgery (5/5) experienced a recurrence.

The effect of the sleeving technique on the occurrence of pseudoaneurysms at anastomosis sites was analyzed and each anastomosis was considered according to the use of a sleeve protection or not. A total of 95 anastomoses were performed, of which 25 were sheathed by a sleeve. The overall pseudoaneurysm rate was 18% (17/95 anastomoses). In the absence of sleeve, the false aneurysm rate was 21% (16/70) but it was only 8% (2/25) in the presence of a sleeve (OR: 2.44; 95% CI (0.89; 6.73)) (p = 0.08) (Figure 4).

Regarding patients who received pre- and postoperative medical treatments without sleeve, the recurrence rate for each anastomosis was 32% (12/38 anastomoses), while patients who received medical treatments and sleeve showed a recurrence rate of only 10% (2/19 anastomoses) (OR: 0.26; 95% CI (0.03; 1.4)) (p = 0.108).

Discussion

We provide here the results of a large series of patients who underwent a vascular procedure for arterial lesions of BD. The postoperative mortality rate was low but we observed a high rate of relapse following surgical procedures comparable to those previously published, although our follow-up of 8.4 years was longer[18-24]. In our series, 51% of BD patients operated for arterial lesions (aneurysms or thrombosis) experienced a relapse which occurred during the first year following surgery in one third of cases.

In previous series, recurrence rates of 50% and 56% and postoperative mortality rates of 14% and 15% have respectively been reported in 32 patients who underwent bypass [25-29] and in 48 patients who underwent graft interposition [22, 26, 28-30].

Device

Vasculitis in BD is distinguishable because both arteries and veins of all sizes are involved. Venous complications are more common than arterial lesions in BD, occurring in 30% of patients [5-7]. VBD patients are at risk of multiple vessel-related complications [9, 27, 31]. Because of the risk of concomitant venous failure due to BD, we did not use the saphenous vein except in specific cases such as distal bypass or septic surgery. In this study, we used saphenous vein grafts in only 13% of cases and the complication rate was of 50%, exclusively due to pseudoaneurysm formation. In fact, results did not significantly differ from those of prosthetic grafts, but these findings should be interpreted with caution because of the small number of venous bypass procedures performed.

The use of prosthetic grafts was associated with a relapse rate of 43%. Thrombosis and pseudoaneurysm occurred after 4/27 (14.8%) and 9/27 (33.3%) procedures, respectively. Thrombosis could be explained by the hypercoagulability secondary to inflammation due to BD in these young patients without atheroma [32].

Arterial allograft could be another option as we observed a lower complication rate of 20%, but in a limited number of cases (1/5 cases).

Arterial wall injury secondary to anastomosis performed between a native artery and a vein or prosthetic graft is a local risk factor for relapse. The endovascular approach has recently been shown to improve results[18] although there may be trauma between a stent and the vascular wall. The endovascular approach was used in only 6% of cases in our study and did not allow concluding to any difference. The endovascular approach could be effective because no anastomosis is needed. The stent should be long enough to cover the lesion in order to seal in a healthy part of the vessel[33]. However, arterial puncture is a risk factor for pseudoaneurysm formation[23, 34, 35] (3 cases in our study). Moreover, data on the long-term results are limited in the literature[36].

Endovascular procedures are also increasingly used in the management of BD, but their superiority has not been demonstrated. Except for Balcioglu et al[37] who have not observed any aneurysm formation nor thrombosis after aortic stent graft placement after a median follow-up of 40 months, all other series have reported a recurrence rate ranging between 8.3 and 75% after endovascular procedures[18-21, 29, 34, 38-40]. Many cases of pseudoaneurysms at the proximal or distal margin of the stent graft have been described[21, 35, 40, 41] and resulted in patient death in three cases due to rupture[19, 29, 40]. Despite the less invasive nature of endovascular treatment, interactions between the stentgraft and the vascular wall led to the formation of pseudoaneurysms at both ends. Yin et al[18] have shown that limiting the oversizing to less than 5% could decrease this risk.

Liu et al[20] have shown better results with bypass surgery than with stent graft in 18 procedures on peripheral arteries. However, the results of aortic aneurysm exclusion were disappointing: among 22 procedures for aortic pseudoaneurysms, a stent graft was used in 19 cases, resulting in recurrence and mortality rates of 18% and 16%, respectively, after a short median follow-up of 23 months. Kim et al[23] have reported the experience of 20 aneurysms in 16 patients treated with stent grafts after a mean follow-up of 4 years. The relapse rate of 19% was low compared to 8 aneurysms in 7 patients who underwent open repair with a relapse rate of 43%.

However, the technique consisting in performing bypass without anastomosis, as described in the Viabahn Padova sutureless technique, could be an option[42].

Relapses

In the present study, the recurrence involved the same arterial anatomical site in 92% of cases. Patients who received perioperative steroids and/or immunosuppressants showed a reduced risk of relapse. In line with previous studies and the European League Against Rheumatism

(EULAR) recommendations[20, 26, 27, 31, 36, 37, 43], anastomotic relapses and graft thrombosis in this series were less common in patients who received aggressive perioperative medical treatment (corticosteroids and immunosuppressants).

In our series, patients were treated preoperatively in only 45% of cases but in these cases, the recurrence rate was significantly reduced compared to that found in untreated patients (28% *versus* 75%). In most cases, BD was not diagnosed at the time of surgery.

The use of postoperative treatments effectively decreased the recurrence rate of arterial lesions.

Many recurrences (24%) occurred during the first year following the surgical procedure but most of them (76%) were delayed with a mean time to recurrence of 6.5 years. These results showed that the risk of recurrence was sustained, whereas in the literature the mean time to recurrence is 10.5 months after a mean follow-up of 6 years[24, 31, 32, 39]. However, there is currently no consensus regarding the postoperative follow-up of these patients. Therefore, extended monitoring with repeated Doppler ultrasound explorations could be useful to detect as soon as possible early and delayed local recurrences or monitoring with CT-scan for thoracic aorta and intrathoracic supra-aortic trunks.

<u>Sleeve anastomosis</u>

We showed that recurrences occurred mainly at the same site, especially anastomotic pseudoaneurysms, even when optimal medical treatment was given. That is why we added a surgical technique to decrease this risk. Sleeve protection of the anastomosis is an easy and reproducible technique consisting in reinforcing arterial anastomosis by wrapping it with a larger prosthetic graft. This technique had previously been described[34, 44] but its effects on the risk of recurrence had never been specifically investigated. In our series, we found that anastomoses protected by a sleeve were less often affected by false aneurysm during the

follow-up than those that were not protected. This extra-arterial reinforcement provides a mechanical support that decreases the risk of secondary anastomotic rupture, although this result was not statistically significant and further studies are needed to confirm it.

This technique was not systematically used when the diagnosis of BD was not suspected at the time of the first surgical procedure or when anastomosis was too close to a collateral artery (such as renal artery or profoundis femoral artery). After a mean follow-up of 8 years, it appeared that the rate of anastomotic false aneurysms was decreased when a sleeve was used. Furthermore, even in patients who received medical treatment, adding a sleeve also decreased the risk of anastomotic false aneurysm. The recurrence rate dropped from 32% to 10% of all anastomoses when a sleeve was associated with the surgical procedure.

The main limitation of this study is its retrospective design. This disease is not common and the diagnosis is often made after the occurrence of one or two arterial events, which limits the possibility of a prospective approach. Moreover, given the small number of patients, the risk of a type 2 statistical error cannot be ruled out. For this reason, we can only conclude that complications tended to decrease when immunosuppressive treatment and the sleeve protection technique were used.

Conclusion

Relapse is a major concern after surgical repair of arterial BD. However, the risk seems to be reduced when medical treatment is used in combination with a vascular procedure. This study suggests the need for targeted perioperative medical management to reduce the risk of arterial recurrence in BD patients. To this end, a multidisciplinary approach combining rheumatologists and vascular surgeons is mandatory.

The use of sleeve anastomosis may reduce the risk of recurrence in the form of anastomotic pseudoaneurysms. However, further studies are needed to confirm its efficacy.

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