ARTERIAL PSEUDOANEURYSM FORMATION AND FEMOROPOPLITEAL STENT FRACTURE AND IN-STENT RESTENOSIS

Ph.D. thesis (short version)

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Budapest
2022

1. Introduction

Minimally invasive endovascular techniques are becoming increasingly popular around the world. Despite being minimally invasive, they can cause systemic, as well as local complications.

Access site-related complications, punctured vessel-related complications, and intervention (site)-related complications are the three types of local complications. There are two sorts of complications associated with punctured vessels: hemorrhagic and non-hemorrhagic. The two most common non-hemorrhagic complications are pseudoaneurysm (PSA) and arteriovenous-fistula.

Most of the local complications occur during or immediately after the procedure, but some complications (particularly those related to the site of intervention: stent fracture [SF] and in-stent restenosis [ISR]) can develop years later.

2. Objectives

My doctoral studies aimed to evaluate early (PSA formation) and late complications of endovascular interventions (femoropopliteal SF and ISR).

2.1. Incidence of and predisposing factors for arterial pseudoaneurysm formation

Since most publications are limited to case series and studies with a small sample size, we aimed to determine the incidence of and identify risk factors for arterial PSA development in a large patient population in a high-volume, multidisciplinary, tertiary center.

2.2. Safety, clinical outcome, and fracture rate of femoropopliteal stenting using 4F compatible delivery system

With the exception of 4-EVER (4F Endovascular Treatment Approach) and PEACE I (Patency Evaluation After Implantation of the 4-French Pulsar-18 Self-Expanding Nitinol Stent in Femoropopliteal Lesions) trials, no comprehensive data have been published on 4F stents in patients with femoropopliteal steno-occlusive disease. Therefore, we aimed to determine the safety, clinical outcome, and fracture rate of femoropopliteal stenting using 4F compatible delivery system.

3. Methods

3.1. Incidence of and predisposing factors for arterial pseudoaneurysm formation

All electronic medical records for PSA development were retrospectively examined at Semmelweis University Heart and Vascular Center in 30,196 patients who underwent any type of radiological or cardiac endovascular procedure requiring arterial puncture. The study covered the period from January 2016 to May 2020. Furthermore, PSAs resulting from procedures where arterial puncture was unintended were also collected.

Endovascular and electrophysiological procedures were conducted by vascular interventional radiologists, invasive cardiologists, or electrophysiologists in a standard manner. Following the procedures, the access site was managed either by manual compression followed by pressure bandaging or by a vascular closure device (VCD).

Color Doppler ultrasound scanning was performed in the presence of pain, swelling, skin changes, and/or bruit at the site of sheath removal or any other abnormality. Patients with PSA received pressure bandage, ultrasound-guided compression (UGC), ultrasound-guided thrombin injection (UGTI), or open surgical repair.

For statistical analysis, R version 4.0.0 (released on April 24, 2020) was used (R Core Team [2020]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

3.2. Safety, clinical outcome, and fracture rate of femoropopliteal stenting using 4F compatible delivery system

Between January 2010 and December 2011, 441 patients underwent femoropopliteal endovascular intervention. In this retrospective study, only 112 consecutive patients with severe claudication (Rutherford–Becker score = 3) or chronic critical limb ischemia (CLI; Rutherford–Becker score = 4–6) who received stenting with a 4F compatible delivery device were examined. The indication for stent implantation was suboptimal angioplasty due to unfavorable morphology of the lesion or failed angioplasty. Vascular interventional radiologists performed all of the stentings. The procedures were performed at the Heart and Vascular Center and at the Department of Radiology and Oncotherapy of Semmelweis University.

Follow-up visits were due 4 weeks, 3–6 months, and 12 months after the procedure, and then once a year. Symptoms were evaluated, femoropopliteal and foot pulses were palpated, and ankle-brachial index (ABI) was measured during follow-up exams. Patients with worsening symptoms, an impalpable popliteal pulse, and an ABI of less than 0.5 were suspected of having a significant ISR. Ultrasonography, computed tomography angiography, and digital subtraction angiography were used to confirm the presence of ISR.

Patients were asked to return for an extra follow-up visit in 2013, during which a fluoroscopic SF evaluation was performed. To visualize the implanted stents, three cine loops with a length of three cardiac cycles (Heart and Vascular Center) or digital X-rays (Department of Radiology and Oncotherapy) were recorded in posteroanterior, and right and left anterior oblique 30–45° projections. Two experienced interventional radiologists assessed the fluoroscopic images in agreement. The Cardiovascular Institute of the South created a nitinol stent fracture classification, which was used to define SFs.

Statistical analysis was performed with SPSS 21.0 software (IBM, Armonk, NY, USA).

4. Results

4.1. Incidence of and predisposing factors for arterial pseudoaneurysm formation

In total, 134 PSAs were found in 134 subjects (women, N=72; men, N=62; mean age: 69.5±15.2 years) during the study period. Invasive vascular radiological procedures produced 53 PSAs (53/6,555 [0.8%]), invasive coronary artery procedures produced 31 PSAs (31/18,038 [0.2%]), and invasive non-coronary artery cardiac procedures produced 25 PSAs (25/5,603 [0.4%]). In addition, 25 PSA cases were caused by inadvertent artery puncture during procedures. The incidence of PSA was found to be significantly different between the vascular radiological and coronary artery groups ($P<0.001$ – chi-squared test), between the vascular radiological and non-coronary artery cardiac groups ($P=0.038$ – chi-squared test), and between the coronary artery and non-coronary artery cardiac groups ($P=0.001$ – chi-squared test). Thirty-four PSAs (25.4%) were identified on the upper extremity arteries, while 100 (74.6%) arose from the lower extremity arteries.

Upper extremity pseudoaneurysms: Sixteen (47.1%) of 34 upper extremity PSAs were observed after invasive vascular radiological procedures, 15 (44.1%) after invasive coronary artery procedures, and three (8.8%) were due to procedures in which the arterial puncture was unintended. The PSA prevalence was 0.05% (10/20,478) in the radial artery, 0.1% (2/1,818) in the ulnar artery, and 1.2% (22/1,897) in the brachial artery. VCD was not used in any of the patients. The PSA sac had a mean diameter of 22.4±14.5 mm and a mean length of 13.1±8.8 mm. The PSA neck measured 2.6±0.8 mm in width and 7.3±7.2 mm in length. Eleven PSAs (32.4%) were treated with replacement of the pressure bandage, four (11.8%) with UGC, 13 (38.2%) with UGTI, and six (17.6%) with open surgical repair. In three cases (8.8%), the PSA was not successfully eliminated in the first try. In two cases, the replacement of the pressure bandage, in one case, the UGTI failed. For those in whom replacing the pressure bandage did not result in the elimination of PSA, UGTI was used as a last resort, while the third patient received interposition grafting. The primary success rate for replacing the pressure bandage was 81.8%, with UGC at

100%, UGTI at 92.3%, and open surgical repair at 100%. No complications were reported during PSA treatments.

Lower extremity pseudoaneurysms: PSAs were found in 37 (37%) of 100 lower extremity patients after invasive vascular radiological procedures, 16 (16%) after invasive coronary artery procedures, 25 (25%) after invasive non-coronary artery cardiac procedures, and 22 (22%) after procedures that resulted in an unintended arterial puncture. The prevalence of femoral artery PSA was 0.4% (99/22,202) in the whole patient group, while it was 2.9% (18/630) in a subgroup of patients with balloon aortic valvuloplasty or transcatheter aortic valve implantation. The prevalence of PSA for the punctured artery with and without VCD use was 37/3,555 (1%) and 97/27,204 (0.4%), respectively (odds ratio [OR], 2.94; 95% confidence interval [CI], 1.95–4.34; $P<0.001$ – chi-squared test). The PSA sac had a mean diameter of 27±16.1 mm and a mean length of 19±11.4 mm. The PSA neck measured 3.3±1.3 mm in width and 10.8±7.1 mm in length. Fourteen PSAs (14%) were treated with replacement of the pressure bandage, one (1%) with UGC, 73 (73%) with UGTI, and 12 (12%) with open surgical repair. In 16 cases (16%), the PSA was not successfully eliminated in the first try. In six cases, the replacement of the pressure bandage, in 10 cases, the UGTI failed. The final solution for those whose PSA did not disappear after the first attempt was either UGTI (N=3) or simple suture of the arterial defect (N=13). The primary success rate for replacing the pressure bandage was 57.1%, with UGC at 100%, UGTI at 86.3%, and open surgical repair at 100%. No complications were reported during PSA treatments.

Comparison of patients with and without pseudoaneurysm: A control group of 134 patients was created to reveal predictors of PSA formation. Controls were randomly selected in a 1:1 fashion matched according to age, gender, and the type of procedure, either from the study population or from our medical record archiving system. A logistic regression model was used to determine which parameters had a significant effect on PSA formation and how strong that effect was. The effect of red blood cell (RBC) count (OR, 0.33; at average international normalized ratio [INR] value), hematocrit (HCT) value (OR, 0.87; at average INR value), hemoglobin (Hb) value (OR, 0.96; at average INR value), INR (OR, 12.97; at average RBC count), the RBC count—INR interaction (OR, 22.28) (or the HCT value—INR interaction [OR, 1.35] or the Hb value—INR interaction [OR, 1.08]), and the RBC count—VCD use interaction (OR, 3.27) (or the HCT value—VCD use interaction [OR, 1.17] or the Hb value—VCD use interaction [OR, 1.05]) on PSA formation was significant. *Figure 1* depicts the single effect of RBC count, HCT, Hb, and INR levels on PSA formation. Neither other laboratory parameters, nor atherosclerotic risk factors and comorbidities, site of the puncture, and size of the sheath used showed correlation with the development of PSA.

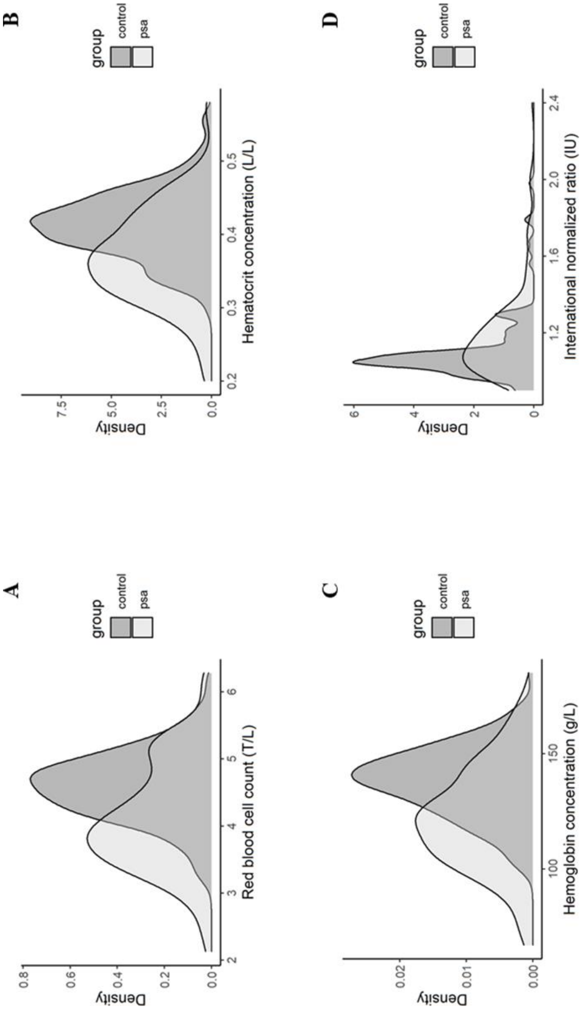


Figure 1. The single effect of red blood cells (A), hematocrit (B), hemoglobin (C), and international normalized ratio (D) on pseudoaneurysm development
Kernel density plots of distributions.

4.2. Safety, clinical outcome, and fracture rate of femoropopliteal stenting using 4F compatible delivery system

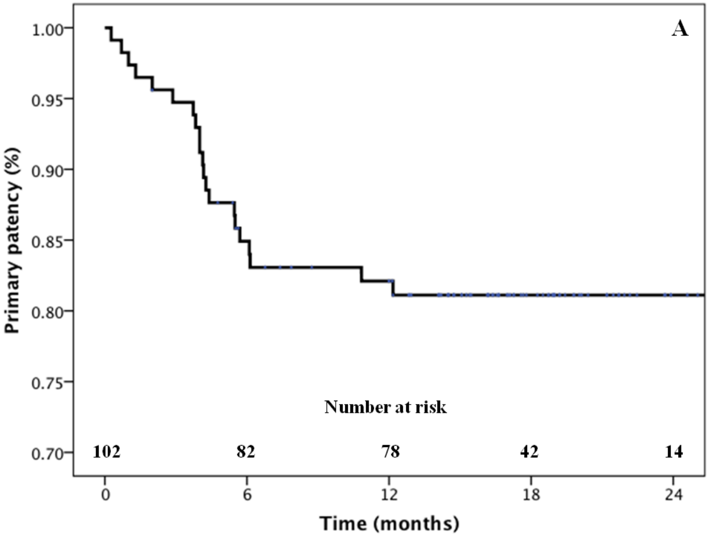
Because 10 patients were lost to follow-up, they were not included in the analysis. The remaining 102 patients (women, N=40; men, N=62) had a mean age of 66.4±10.1 years. Severe claudication was the reason for femoropopliteal revascularization in 63 patients (61.8%) and chronic CLI in 39 patients (38.2%).

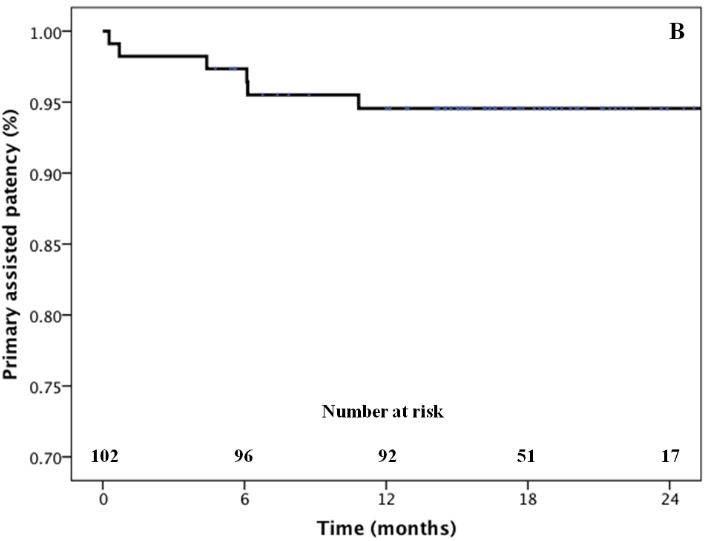
A total of 114 lesions were treated. In 87 cases (76.3%), the lesions were *de novo* stenoses, and in 27 cases (23.7%), the lesions were restenoses after previous angioplasty. Sixty-four (56.1%) of the lesions treated were stenoses, whereas 50 (43.9%) were total occlusions. In 49 cases (43%), the lesions were long and in 35 cases (30.7%), they were heavily calcified. Long lesions were those that were longer than 100 mm, while heavily calcified lesions were those with calcification apparent on fluoroscopy more than 75% of the length of the stenotic or occluded segment. The side distribution of the lesions was almost equal (left, N=58; right, N=56). Lesions were located in the superficial femoral artery in 36 cases (31.6%), in the femoropopliteal transitional zone in 47 (41.2%), and in the popliteal artery in 31 (27.2%). According to the TransAtlantic Inter-Society Consensus (TASC) classification, the lesions were TASC–A, TASC–B, TASC–C, and TASC–D in 35 (30.7%), 34 (29.8%), 30 (26.3%), and 15 cases (13.2%), respectively.

A total of 119 stents were implanted. All patients received self-expanding nitinol stents (Astron Pulsar, N=42; Pulsar-18, N=77; Biotronik AG, Bülach, Switzerland). Forty-six (38.7%) of the deployed stents were long and 10 (8.4%) were implanted in a partially overlapping position. Stents with a length of 120 mm or more were considered long. In 17 patients (16.7%), below the knee interventions were also performed.

The technical success rate, which was defined as <30% residual stenosis without dissection or extravasation, was 100%. Two patients (2%) developed PSA at the femoral puncture site, and both were treated with UGTI. The 30-day all-cause mortality rate was zero. Minor amputations were performed on five individuals (4.9%).

The mean follow-up time was 25.3±6.2 months. Eleven patients (10.8%) died during the follow-up period (acute myocardial infarction, N=4; stroke, N=2; and malignancy, N=5). Significant (≥70%) ISR was observed in 21 patients (20.6%). Target lesion revascularization was carried out in 15 patients (14.7%; angioplasty, N=13 and stenting, N=2), while target vessel revascularization was performed in six patients (5.9%; angioplasty, N=3; stenting, N=1; and open surgery, N=2). Major amputation was necessary in nine patients. Indications for amputation were acute ischemia in four cases and chronic ischemia in five cases. All stents were patent in the below the knee amputation group, while all stents were blocked in the above the knee amputation group. The primary, primary assisted, and secondary patency rates were 83.1%, 97.2%, 86.2%, respectively, at 6 months and 80.4%, 94.3%, 85.4%, respectively, at 12 months. (*Figure 2*)


A
Primary patency (%)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Number at risk
102
82
78
42
14
0
6
12
18
24
Time (months)


B
Primary assisted patency (%)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Number at risk
102
96
92
51
17
0
6
12
18
24
Time (months)

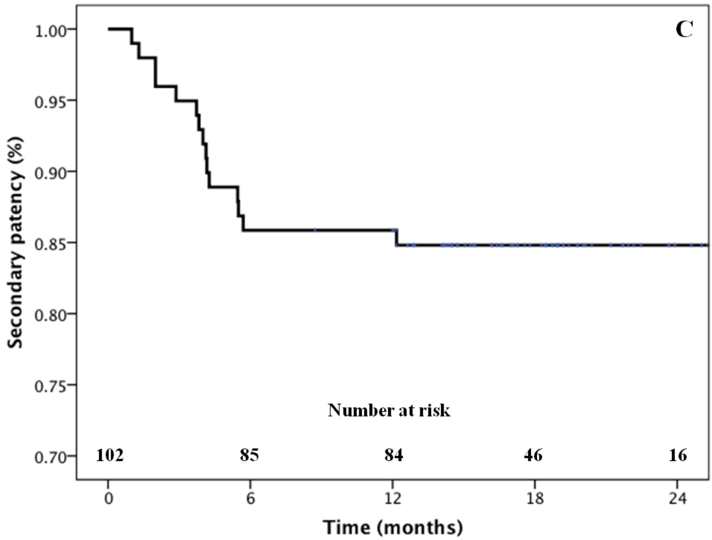


Figure 2. Primary (A), primary assisted (B), and secondary patency rates (C)
Kaplan–Meier curves.

The mean Rutherford–Becker classification improved from 3.9±1.1 before the procedure to 2.1±1.4 at the most recent follow-up (P<0.001 – Mann–Whitney *U* test). The mean resting ABI improved from 0.5±0.1 before the procedure to 0.8±0.2 at the most recent follow-up (P<0.001 – Student *t*-test).

Patients who died or underwent above the knee amputation and who had stents that were placed during the follow-up were excluded from the analysis of SF. A total of 104 stents were analyzed. In 87 patients, 27 SFs (26%) were found: type I (*single strut fracture*) in nine cases, type II (*multiple strut fractures at different sites in the stent*) in eight cases, type III (*multiple strut fractures* *resulting in complete transverse stent fracture*) in five cases, and type IV (*complete transverse fracture with stent separation*) in five cases. In 83% of the stents, the fracture was localized to their middle part. The number of patients with ISR (occurring at any time throughout the follow-up) was significantly higher in the fractured group than in the non-fractured group (N=15 versus N=2; P<0.001 – chi-squared test) at the time of the fluoroscopic study.

Univariate logistic regression analysis revealed that stents placed in popliteal 1–2 location were associated with an increased incidence of ISR (OR, 3.83; 95% CI, 1.10–13.31; P=0.030). Calcified, especially heavily calcified lesions were found to be predictive of SF (OR, 19.64; 95% CI, 4.31–89.47; P<0.001 and OR, 116.07; 95% CI, 22.57–597.03; P<0.001, respectively).

5. Conclusions

5.1. Incidence of and predisposing factors for arterial pseudoaneurysm formation

The prevalence of PSA was highest after radiological procedures. Patients in whom the puncture site is closed with a VCD require increased observation. Preprocedural laboratory findings are useful for the identification of patients at high risk of PSA formation.

5.2. Safety, clinical outcome, and fracture rate of femoropopliteal stenting using 4F compatible delivery system

The complication rate of femoropopliteal stenting using a 4F compatible delivery system is low, the 12-month patency rate is good, and the SF rate is acceptable.

6. Bibliography of the candidate's publications

6.1. Peer reviewed articles with relevance to the current work

1. Sarkadi H, Csőre J, Veres DS, Szegedi N, Molnár L, Gellér L, Bérczi V, Dósa E. (2021) Incidence of and predisposing factors for pseudoaneurysm formation in a high-volume cardiovascular center. PLoS One, 16: e0256317. **IF: 3.240**

2. Sarkadi H, Bérczi V, Kollár A, Kiss D, Jakabfi P, Végh EM, Nemes B, Merkely B, Hüttl K, Dósa E. (2015) Safety, clinical outcome, and fracture rate of femoropopliteal stenting using a 4F compatible delivery system. Eur J Vasc Endovasc Surg, 49: 199–204. **IF: 2.912**

6.2. Other peer-reviewed articles

1. Bérczi Á, Nguyen TD, **Sarkadi H**, Nyárádi BB, Beneda P, Szőnyi Á, Philippovich M, Szeberin Z, Dósa E. (2022) Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors. J Vasc Surg, submitted. **IF: 4.268**

2. Bérczi Á, Kaposi NP, **Sarkadi H**, Péter Cs, Bérczi V, Dósa E. (2021) Vascular procedures during the COVID-19 pandemic in a high volume Eastern European interventional radiology department. IMAGING, 13: 138–141. **IF: -**

3. Dósa E, Nemes B, Bérczi V, Novák PK, Paukovits TM, **Sarkadi H**, Hüttl K. (2014) High frequency of brachiocephalic trunk stent fractures does not impair clinical outcome. J Vasc Surg, 59: 781–785. **IF: 3.021**

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mineral density is associated with site-specific atherosclerosis in patients with severe peripheral artery disease. Calcif Tissue Int, 93: 55–61. **IF: 2.748**

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6. Krepuska M, Szeberin Z, Sótonyi P, **Sarkadi H**, Fehérvári M, Apor A, Rimely E, Prohászka Z, Acsády G. (2011) Serum level of soluble Hsp70 is associated with vascular calcification. Cell Stress Chaperones, 16: 257–265. **IF: 3.013**

7. Szeberin Z, Fehérvári M, Krepuska M, Apor A, Rimely E, **Sarkadi H**, Bíró G, Sótonyi P, Széplaki G, Szabolcs Z, Prohászka Z, Kalabay L, Acsády G. (2011) Fetuin-A serum levels in patients with aortic aneurysms of Marfan syndrome and atherosclerosis. Eur J Clin Invest, 41: 176–182. **IF: 3.018**