University of Crete
School of Medicine
Division of Medical Imaging
Department of Radiology
Head: Prof. A. Karantanas

Doctoral Thesis

"The Role of Percutaneous Angioplasty in the Management of Chronic Lower Limb Ulcers of Arterial Aetiology"

Supervisor: Dimitrios Tsetis
Professor of General Radiology / Interventional Radiology

Elias Kehagias-Athanasopoulos

Heraklion, Crete, June 2020

Supervisor

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Three-member Advisory Commitee

D. Tsetis, Professor of Radiology

N. Gourtsoyiannis, Emer. Professor of Radiology

C. Ioannou, Assoc. Professor of Vascular Surgery

Seven-member Examining Commitee

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N. Gourtsoyiannis, Emer. Professor of Radiology

C. Ioannou, Assoc. Professor of Vascular Surgery

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E. de Bree, Professor of Surgical Oncology

I. Damilakis, Professor of Medical Physics

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Ηράκλειο Κρήτης, Ιούνιος 2020

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Τριμελής Συμβουλευτική Επιτροπή

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Α. Καραντάνας, Καθηγητής Ακτινολογίας

Γ. Κοχιαδάκης, Καθηγητής Καρδιολογίας

Ε. de Bree, Καθηγητής Χειρουργικής Ογκολογίας

Ι. Δαμηλάκης, Καθηγητής Ιατρικής Φυσικής

To my parents

To my wife and children

FOREWORD

This PhD thesis was completed in the Interventional Radiology Unit and in the Department of Vascular Surgery of Heraklion University Hospital, at the University of Crete Medical School, in Heraklion, Crete, Greece.

The subject was inspired by Prof. Dimitrios Tsetis, head of the Interventional Radiology Unit. Our findings provide new insights on healing of chronic lower limb ulcers of arterial aetiology using percutaneous transluminal angioplasty (PTA) as primary treatment method. Patients included in this study suffered from chronic lower limb ulcers, non-pulpable or diminished peripheral pulses and visited the Vascular Surgery Clinic of our hospital. Based on previous reports on the promising results peripheral angioplasty and stenting techniques demonstrated in lower limb salvage, we conducted a prospective study to investigate the feasibility, safety and effectiveness of these techniques on lower limb ulcer healing and limb salvage in patients with critical limb ischemia (CLI). This is an original study in consecutive patients presented with lower limb ulcers in our hospital. Our results support our primary hypothesis that percutaneous angioplasty promotes healing of lower limb arterial ulcers.

Concluding this long, team project, I would like to thank all the persons who took part on it. I would like to express my deepest graditude to my professor and mentor, D. Tsetis, for his inspiration and guidance. This tedious effort wouldn't be possible without his commitment and patience. Working under his expert guidance was an honour and a privilege for me. To Prof. C. Ioannou I would like to extend my deepest appreciation for his valuable assistance, commitement and guidance through all those years. Beeing the head of the Vascular Surgery, his contribution was invaluable in patient recruitement, admission, follow-up, as long as management of complications and patients needing surgery. Our team was fortunate enough to have brilliant junior members, like N. Kontopodis, E. Papadaki and N. Galanakis, who had

the burden of following-up patients and collecting data, and to whom I am deeply endebed. Above all, my deepest gratitude belongs to Prof. Emer. N. Gourtsoyiannis, a mentor of mine and many others, who inspired a generation of doctors to pursue Radiology and offered me the opportunity to be a part of this team. Lastly, I thank my parents for teaching me with their example to never give up, and my wife Dr. Izolde Bouloukaki, for her invaluable assistance, patience and understanding.

Elias Kehagias, Heraklion, March 2020

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PERSONAL INFORMATION

- Date of birth: 13th May 1973
- Age: 47
- Place of Birth: Athens, Greece
- Nationality: Greek
- Marital status: Married
- Children: 1 daughter (11), 1 son (9)

EDUCATION

February 9-March 20, 2015
Christiana Care Hospital, Newark, Delaware, USA
Observer attachment in Vascular and Interventional Radiology

January 2013 Athens, Greece
Certification of Completion of Subspecialty Training in Interventional Radiology *(issued by the Greek Ministry of Health)*

March 2009-Present Heraklion, Crete, Greece
Postgraduate PhD student, in Interventional Radiology at the University of Crete, School of Medicine
Title: "The role of percutaneous angioplasty in the management of chronic limb ulcers of arterial aetiology"

December 2008
Sotiria Hospital, Athens, Greece
Observer attachment in non-Vascular Interventional Radiology *(CT-guided procedures: biopsies, drainage, ablations)*

February 2006 Heraklion, Crete, Greece
Certification of Completion of Specialty Training in Radiology *(issued by the Greek Ministry of Health)*

September 1992-November 1998 Patras, Greece
University of Patras, School of Medicine
Degree: Medical Degree ("Ptycheion Iatrikes")

September 1991-September 1992
University of Patras, School of Pharmacy Patras, Greece

PROFESSIONAL EXPERIENCE

July 2008 – **Present**
Heraklion University Hospital Heraklion, Crete, Greece
Department of Angiography and Interventional Radiology
Interventional Radiology Consultant

Main areas of expertise are peripheral diagnostic angiographies PTA and stenting, liver TACE, elective and emergent embolisation procedures, Percutaneous Endovascular Aortic Repair, central venous access and non-vascular procedures, (PTCD, image guided RF/MW ablation for liver and kidney lesions, biopsies and drainage procedures, ureteral stenting)

May 2007 – May 2008
Agios Nikolaos General Hospital Agios Nikolaos, Crete, Greece
Department of Radiology
Radiology Consultant

Performed diagnostic radiology, screening mammography, ultrasound colour-Doppler and CT examinations

April 2006 – April 2007
Rethymnon General Hospital Rethymnon, Crete, Greece
Department of Radiology
Radiology Consultant

Performed diagnostic radiology, ultrasound colour-Doppler and CT examinations

November 2000 – November 2005 Heraklion, Crete, Greece
Venizelion General Hospital – Heraklion University Hospital
Department of Radiology
Radiology Registrar

March 2000 – October 2000 Hania, Crete, Greece
Kissamos Health Centre
Obligatory service as a Countryside Doctor

March 1999 – March 2000 Soufli, Evros, Greece
514 Infantry Regiment

Obligatory military service as a Doctor in Greek Military

November 1998 – March 1999 Kalamata, Greece
Kalamata General Hospital
Department of Orthopaedics
Observer Attachment

PUBLICATIONS / BOOK CHAPTER CONTRIBUTION / REVIEWER EXPERIENCE

32) Aggressive recurrence of Non-Hodgkin's Lymphoma after successful clearance of hepatitis C virus with direct acting antivirals.
Samonakis DN, Psyllaki M, Pavlaki KI, Drakos E, **Kehagias E**, Tzardi M, Papadaki HA. Ann Hepatol. 2019 Oct 3. pii: S1665-2681(19)32247-1. doi: 10.1016/j.aohep.2019.08.012. [Epub ahead of print]

31) Feasibility of ischemic leg ulcer healing using percutaneous techniques: a real-life study.
Kehagias E, Ioannou CV, Bouloukaki I, Papadaki E, Galanakis N, Kontopodis N, Tsetis D. Acta Radiol. 2019 Jul 18:284185119862955. doi: 10.1177/0284185119862955. [Epub ahead of print]

30) Transcatheter arterial chemoembolization combined with radiofrequency or microwave ablation for hepatocellular carcinoma: a review.
Galanakis N, **Kehagias E**, Matthaiou N, Samonakis D, Tsetis D.
Hepat Oncol. 2018 Sep 28;5(2):HEP07. doi: 10.2217/hep-2018-0001. eCollection 2018 Apr. Review.

29) The "Arm-to-Chest Tunneling" technique: A modified technique for arm placement of implantable ports or central catheters.
Kehagias E, Tsetis D. J Vasc Access. 2019 Nov;20(6):771-777. doi: 10.1177/1129729819826039. Epub 2019 Apr 3.

28) CT Foot Perfusion Examination for Evaluation of Percutaneous Transluminal Angioplasty Outcome in Patients with Critical Limb Ischemia: A Feasibility Study.
Galanakis N, Maris TG, Kontopodis N, Ioannou CV, **Kehagias E**, Matthaiou N, Papadakis AE, Hatzidakis A, Perisinakis K, Tsetis D. J Vasc Interv Radiol. 2019 Apr;30(4):560-568. doi: 10.1016/j.jvir.2018.10.018.

27) Occupational exposure during endovascular aneurysm repair (EVAR) and aortoiliac percutaneous transluminal angioplasty (PTA) procedures.
Tzanis E, Tsetis D, **Kehagias E**, Ioannou CV, Damilakis J. Radiol Med. 2019 Jun;124(6):539-545. doi: 10.1007/s11547-018-00985-8. Epub 2019 Jan 23.

26) Incidence and Endovascular Treatment of Isolated Atherosclerotic Popliteal Artery Disease: Outcomes from the IPAD Multicenter Study.
Spiliopoulos S, Kitrou P, Galanakis N, Papadimatos P, Katsanos K, Konstantos C, Palialexis K, Reppas L, **Kehagias E**, Karnabatidis D, Brountzos E, Tsetis D. Cardiovasc Intervent Radiol. 2018 Oct;41(10):1481-1487. doi: 10.1007/s00270-018-2028-7. Epub 2018 Jul 10**.**

25) Foreign body mimicking neoplasia of the renal pelvis on magnetic resonance imaging.
Mamoulakis C, Gorgoraptis P, **Kehagias E**, Karantanas A. Turk J Urol. 2018 Jan;44(1):82-86. doi: 10.5152/tud.2017.67366. Epub 2017 Dec 19.

24) Ultrasound-guided direct intrahepatic portosystemic shunt in patients with Budd-Chiari syndrome: Short- and long-term results.
Hatzidakis A, Galanakis N, **Kehagias E**, Samonakis D, Koulentaki M, Matrella E, Tsetis D. Interv Med Appl Sci. 2017 Jun;9(2):86-93. doi: 10.1556/1646.9.2017.2.14.

23) Proper technique of port puncture in the deltopectoral groove: the "port pinning technique".
Kehagias E, Tsetis D. J Vasc Access. 2017 Jan 18;18(1):e10. doi: 10.5301/jva.5000635.

22) Direct Stenting in Patients with Acute Lower Limb Arterial Occlusions: Immediate and Long-Term Results.
Galanakis N, Kontopodis N, Peteinarakis I, **Kehagias E**, Ioannou CV, Tsetis D. Cardiovasc Intervent Radiol. 2017 Feb;40(2):192-201. doi: 10.1007/s00270-016-1500-5. Epub 2016 Nov 8.

21) Current role of microwave ablation in the treatment of small hepatocellular carcinomas.
Lucchina N, Tsetis D, Ierardi AM, Giorlando F, Macchi E, **Kehagias E**, Duka E, Fontana F, Livraghi L, Carrafiello G. Ann Gastroenterol. 2016 Oct-Dec;29(4):460-465. Epub 2016 Jun 24. Review.

20) Routine use of an aortic balloon to resolve

possible inflow stenosis induced by the inflatable ring fixation mechanism of the Ovation endograft.
Ioannou CV, Kontopodis N, Georgakarakos E, **Kehagias E**, Metaxa E, Lioudaki S, Papaharilaou Y, Tsetis D. Radiol Med. 2016 Nov;121(11):882-889. Epub 2016 Jul 23.

19) Symptomatic exercise-induced complete atrioventricular block due to severe superior vena cava stenosis.
Simantirakis E, Marketou M, **Kehagias E**, Kanoupakis E, Hamilos M, Vardas P. Int J Cardiol. 2016 Jul 15;215:167-8. doi: 10.1016/j.ijcard.2016.04.123. Epub 2016 Apr 16. No abstract available.

18) ePTFE stent graft in non-steno-occlusive arterial disease: 2 centers retrospective study.
Ierardi AM, **Kehagias E**, Piffaretti G, Piacentino F, De Marchi G, Tozzi M, Ioannou C, Tonolini M, Magenta Biasina A, Carrafiello G, Tsetis D. Radiol Med. 2016 Jun;121(6):482-93. doi: 10.1007/s11547-016-0623-8. Epub 2016 Feb 16.

17) The "L-shaped tunneling technique": a modified technique facilitating a more discreet implantable port positioning
Elias Kehagias, Dimitrios Tsetis. J Vasc Access 2016 Mar-Apr

16) Percutaneous rheolytic mechanical thrombectomy in thrombosed direct intrahepatic portosystemic shunt: Report of two cases
Dimitrios Tsetis, **Elias Kehagias,** Dimitrios Samonakis, Elias Kouroumalis, Adam Hatzidakis. Interventional Medicine and Applied Science 7(4):171-175 · December 2015

15) Acute TIPS occlusion due to iatrogenic arteriovenous shunt in a cirrhotic patient with total portal vein thrombosis
Adam Hatzidakis, Elias Kouroumalis, **Elias Kehagias,** Emmanuel Digenakis, Dimitrios Samonakis, Dimitrios Tsetis. Interventional Medicine and Applied Science 7(4):166-170 · December 2015

14) Intraoperative Endovascular Stent-graft Repair of a Popliteal Artery Laceration and Occlusion during Total Knee Arthroplasty
Elias Kehagias, Christos V Ioannou, Nikolaos Kontopodis, Constatinos Balalis, Dimitrios Tsetis. Annals of

Vascular Surgery 06/2015;
DOI:10.1016/j.avsg.2015.04.081 · 1.17 Impact Factor

13) Endovascular Aneurysm Repair with the Ovation Trivascular Stent Graft System Utilizing aPredominantly Percutaneous Approach Under Local Anesthesia
Christos V Ioannou, Nikolaos Kontopodis, **Elias Kehagias,** Alexia Papaioannou, Alexandros Kafetzakis, George Papadopoulos, Dimitrios Pantidis, Dimitrios Tsetis. The British journal of radiology 05/2015; 88(1051):20140735. DOI:10.1259/bjr.20140735 2.03 Impact Factor

12) Totally Percutaneous Endovascular Aneurysm Repair Using the Preclosing Technique
Nikolaos Kontopodis, Dimitrios Tsetis, **Elias Kehagias**, Nikolaos Daskalakis, Nikolaos Galanakis, Christos V Ioannou. Surgical laparoscopy, endoscopy & percutaneous techniques 05/2015; 25(4). DOI:10.1097/SLE.0000000000000176 · 1.14 Impact Factor

11) Bifurcated Aortoiliac Endograft Limb Occlusion during Deployment and Its Bailout Conversion Using the External Iliac Artery to Internal Iliac Artery Endograft Technique
Elias Kehagias, Nikolaos Kontopodis, Dimitrios Tsetis, Christos V. Ioannou. Annals of Vascular Surgery 03/2015; 29(5). DOI:10.1016/j.avsg.2015.01.026 · 1.17 Impact Factor

10) Graft Inflow Stenosis Induced by the Inflatable Ring Fixation Mechanism the Ovation Stent-Graft System: Hemodynamic and Clinical Implications
Christos V Ioannou, Nikolaos Kontopodis, Eleni Metaxa, Yannis Papaharilaou, Efstratios Georgakarakos, Alexandros Kafetzakis, **Elias Kehagias,** Dimitrios Tsetis. Journal of Endovascular Therapy 12/2014;21(6):829-38.DOI:10.1583/14-4771MR.1 3.35 Impact Factor

9) Management of renal arteriovenous malformations: A pictorial review
Adam Hatzidakis, Michele Rossi, Charalampos Mamoulakis, **Elias Kehagias,** Gianluigi Orgera, Miltiadis Krokidis, Apostolos Karantanas Insights into Imaging 07/2014; 5(4). DOI:10.1007/s13244-014-0342-4

8) Focal aorto-iliac atherosclerosis amenable to endovascular interventions though considered benign carry a significant risk of cardiovascular mortality
Ioannou CV, Kostas T, Kontopodis N, Manousaki E,

Chlouverakis GI, **Kehagias E,** Tsetis DK. Int Angiol. 2014 May 13.

7) Transcatheter embolisation of iatrogenic renal vascular injuries
Ierardi AM, Floridi C, Fontana F, Duka E, Pinto A, Petrillo M, **Kehagias E,** Tsetis D, Brunese L, Carrafiello G. Radiol Med. 2014 Apr;119(4):261-8. doi: 10.1007/s11547-013-0343-2. Epub 2013 Dec 3.

6) Vibrational angioplasty in recanalization of chronic femoropopliteal arterial occlusions: single center experience
Kapralos I, **Kehagias E,** Ioannou C, Bouloukaki I, Kostas T, Katsamouris A, Tsetis D. Eur J Radiol. 2014 Jan;83(1):155-62. doi: 10.1016/j.ejrad.2013.09.026. Epub 2013 Oct 8

5) ePTFE coated self-expanding Nitinol Stent in the treatment of non-obstructive peripheral arterial lesions
AM Ierardi, **E Kehagias,** P Filippo, M Petrillo, N Lucchina, C Floridi, G Piffaretti, C Ioannou, G Carrafiello, D Tsetis. Experimental and clinical cardiology 20(6):4113-4132 January 2014 0.76 Impact Factor

4) Common and uncommon complications of totally implantable central venous ports: A pictorial essay
Perdikakis E, **Kehagias E,** Tsetis D. J Vasc Access. 2012 Jul-Sep;13(3):345-50. doi: 10.5301/jva.5000055.

3) Percutaneous retrieval of a misplaced guidewire from the sigmoid dural venous sinus
Perdikakis E, **Kehagias E,** Tsetis D. Chirurgia 2011 December;24(6):349-51

2) Endovascular Treatment of an Inferior Vena Cava Stenosis Caused by Retroperitoneal Fibrosis with the Use of a Self-expandable Nitinol Stent
Perdikakis E, **Kehagias E,** Tsetis D. Eur J Vasc Endovasc Surg 01/2011; 41(5):714-714. DOI:10.1016/ j.ejvs.2011.01.026

1) US appearance of a Late-diagnosed Left Bochdalek Hernia in a Middle-aged Woman: Case Report and Review of the Literature
S Megremis, N Segkos, G Gavridakis, M Mattheakis, **E Kehayas**, L Triantafyllou, E Sfakianaki, G Chalkiadakis. J Clin Ultrasound, 2005 Oct;33(8):412-7. PMID: 16240423

Book chapter contributor

Endovascular Interventions A Case-Based Approach
(Contributor) Editors: Robert S. Dieter, Raymond A. Dieter, Jr., Raymond A. Dieter, III ISBN: 978-1-4614-7311-4 (Print) 978-1-4614-7312-1 (Online), Springer Science+Business Media, New York 2014

Online CIRSE Academy Course contributor

CIRSE Academy Online Courses: Central Vascular Access
T. Rodt, **E. Kehagias**
Published online at: https://www.cirse.org/product/central-venous-access-online-course/

Reviewer Experience

Reviewer for the Cardiovascular and Interventional Radiology journal (CVIR)
Reviewer for the Diagnostic and Interventional Radiology journal (DIR)
Reviewer of CIRSE Academy on-line courses

PRESENTATIONS

Selected Oral Presentations

Last option catheter access – New techniques for tunnelling
E. Kehagias
Endovascular Access Meeting
21-22 June 2019, Patras, Greece

Treatment of Hemorrhoidal Disease
E. Kehagias
11th Congress of the Greek Society of Interventional Radiology
17-19 May 2019, Athens, Greece

Vascular Dysplasias: Current Treatment
E. Kehagias
Greek Congress of Dermatology
25-28 June 2015, Thessaloniki, Greece

Treatment of Postpartum Bleeding
E. Kehagias
7th Congress of the Greek Society of Interventional Radiology
15-17 May 2015, Athens, Greece

Future Aproach for IV Therapy
Bard Access Advisory Board
May 8th, 2013, London, UK

Ureteral Stenting for Obstructive Uropathy

E. Kehagias

6th Congress of the Greek Society of Interventional Radiology

11-13 May 2012, Patras, Greece

Advanced Disaster Session

E. Kehagias

5th MACOVA (Multidisciplinary Advanced Course On Venous Access), 19 – 21 October 2011, Barcelona, Spain

Percutaneous treatment of malignant superior vena cava syndrome using nitinol self-expandable stents

E. Kehagias, A. Vasilogiannakis, I. Kapralos, D. Tsetis, N. Gourtsoyiannis

7th Balkan Congress of Radiology (BCR), 18 – 22 November 2009, Istanbul, Turkey

Transcatheter embolization in acute bleeding of craniofacial area

Konstantinos Psaras, **Elias Kehagias,** Ioannis Kapralos, Dimitrios Tsetis, Nikolaos Gourtsoyiannis

7th Balkan Congress of Radiology (BCR), 18 – 22

November 2009, Istanbul, Turkey

PTCD complications in patients with benign and malignant biliary stenoses

E. Kehagias, E. Drakonaki, A. Hatzidakis, E. Haronitakis, G. Patramanis, N. Philipakis, D. Tsetis, N. Gourtsoyiannis

Oral presentation at the XIV Greek Congress of Radiology, 29 September – 2 October 2004, Athens, Greece

Value of preinterventional imaging before transjugular intrahepatic portosystemic shunt. Comparison of color-Doppler and magnetic resonance-imaging/magnetic resonance-portography

A. Hatzidakis, O. Papakonstantinou, C. Koulieraki, D. Tsetis, **E. Kehagias,** K. Fragos, E. Charonitakis, N. Gourtsoyiannis

CIRSE, 25-29 September 2004, Barcelona, Spain

Selected Poster Presentations

Cases-of-the-Day Presentation: Rendu-Osler-Weber syndrome

E. Kehagias, I. Kapralos, D. K. Tsetis, N. Gourtsoyiannis

On-line poster presentation (EPOS) at the European Congress of Radiology (ECR) 2009 meeting, 6-10 March 2009, Vienna, Austria

Extended field-of-view two dimentional ultrasonography of the neck : improvement in lesion documentation

A. Andrianaki, **E. Kehagias**, S. Megremis, E. Agianniotakis, N. Segkos, M. Matthaiakis, E. Sfakianaki

On-line poster presentation (EPOS) at the 17th European Congress of Head and Neck Radiology, 7-9 October 2004, Paris, France

Assessment of skeletal age with hand and wrist sonography: Could a standardized method replace radiography?

S. Megremis, G. Cavallo, M. Michalakou, **E. Kehayas**, N. Segkos, E. Agianniotakis, E. Sfakianaki

On-line poster presentation (EPOS) at the ECR 2004 meeting, 5-9 March 2004, Vienna, Austria

CONGRESSES – SEMINARS ATTENDED

Selected international congresses attended

Balkan Congress of Radiology

17-19 October 2019, Heraklion, Greece

European Conference on Embolotherapy

26- 29 June 2019, Valencia, Spain

ESIR 2019, Prostate Embolization

14-15 June 2019, Milan, Italy

ESIR 2019, DVT/PE Thrombolysis and

Thrombectomy

15-16 February 2019, Dublin, Ireland

European Conference of Interventional Oncology

22-25 April 2018, Vienna, Austria

Interdisciplinary Endovascular Aortic Symposium

23-25 September 2018, Lisbon, Portugal

Annual meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)

22-25 September 2018, Lisbon, Portugal

Annual meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)

26-30 September 2015, Lisbon, Portugal

18th European Vascular Course (EVC)
12-14 May 2014, Maastricht, Netherlands

Leipzig Inteventional Course (LINC)
28-31 January 2014, Leipzig, Germany

European School of Interventional Radiology (ESIR) 2013 Musculoskeletal Interventions Course
7-8 June 2013, Athens, Greece

Annual meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)

15-19 September 2012, Lisbon, Portugal

ESIR 2012 Embolisation
20-21 April 2012, Athens, Greece

5th Multidisciplinary Advanced Course On Venous Access (MACOVA)
19-21 October 2011, Barcelona, Spain

4th Multidisciplinary Advanced Course On Venous Access (MACOVA)
20-22 October 2010, London, UK

Annual meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)
2-6 October 2010, Valencia, Spain

ESIR 2010 Advanced Vascular Course

25-26 June 2010, London UK

7th Balkan Congress of Radiology (BCR)

18-22 November 2009, Istanbul, Turkey

Annual meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)
19-23 September 2009, Lisbon, Portugal

ESIR 2009 Basic Vascular Course
24-25 July 2009, Heraklion, Crete, Greece

ESGAR Image guided ablation workshop
25-26 March 2009, London, UK

European Congress of Radiology (ECR) 2009
6-10 March 2009, Vienna, Austria

ESIR 2008 Interventional Treatment of Peripheral Arterial Disease Hands-On Course
27-28 November 2008, Diegem, Belgium

ESIR 2008 Carotid and Renal Stenting Course
31 October-1st November 2008, Prague, Czech Republic

ESIR 2008 Non-Vascular Upper GI Interventions Course
10-11 October 2008, Novi-Sad, Serbia

Annual meeting of the Cardiovascular and

Interventional Radiological Society of Europe (CIRSE)
13-17 September 2008, Copenhagen, Denmark

ESIR 2008 Image-Guided Radiofrequency Tumor Ablation Course
18-19 July 2008, Heraklion, Crete, Greece

European Congress of Radiology (ECR) 2008
7-11 March 2008, Vienna, Austria

European Breast Imaging Update 2008
March 6th 2008, Vienna, Austria

5th Aegean Postgraduate Radiology Course
28-30 September 2007, Heraklion, Crete, Greece

European School of Radiology (ESOR) – GALEN course on Oncologic Imaging
29 June-1 st July 2007, Heraklion, Crete, Greece

ESIR 2007 Non-Vascular Upper GI Interventions Course
22-23 June 2007, Heraklion, Crete, Greece

17th Annual Meeting of ESTI (European Society of Thoracic Imaging)
8-10 June 2007, Athens, Greece

7th Athenian Days of Interventional Radiology Cardiac and Vascular imaging Workshop - "hands on" course (MRI and Volumetric CT)
17-19 May 2007, Athens, Greece

European Congress of Radiology (ECR) 2007
9-13 March 2007, Vienna, Austria

European Breast Imaging Update 2007
March 8th 2007, Vienna, Austria

ESMRMB School of MRI – Clinical Course on Advanced MR imaging of the Muskuloskeletal System
29 June-1 July 2006, Heraklion, Crete, Greece

17th Annual Meeting and Postgraduate Course of ESGAR (European Society of Gastrointestinal and Abdominal Radiology) and 35th Annual Meeting of SGR (Society of Gastrointestinal Radiologists)

19-23 June 2006, Heraklion, Crete, Greece

PROFESSIONAL MEMBERSHIPS

Member of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) (**2008- Present**)

Member of the Greek Society of Interventional Radiology

Member of the Greek Society of Radiology

ACCREDITATIONS

January 2013 Athens, Greece
Certification of Completion of Subspecialty Training in Interventional Radiology, (issued by the Greek Ministry of Health)

October 2010 Valencia, Spain
European Board of Interventional Radiology, (EBIR)
Passed

August 2009 Heraklion, Crete, Greece
"Conscious Sedation" Health Sciences Education Online Course, University of Louisville, Kentucky, USA
Passed

February 2006 Heraklion, Crete, Greece
Certification of Completion of Specialty Training in Radiology, (issued by the Greek Ministry of Health)

September 2005 London, UK
Final Examination for the Fellowship of the Royal College of Radiologists, (FRCR) Module 1 (Chest-Cardiovascular)
Passed

June 2005 London, UK
First Examination for the FRCR (Radiation Physics, Radiation Protection, Radiation Protection Legislation)

Passed

August 1998 Athens, Greece

United States Medical Licensing Examination Step 2

Passed

October 1996 Athens, Greece

United States Medical Licensing Examination Step 1

Passed

LANGUAGES

Greek (Native language)

English

Test of English as a Foreign Language (TOEFL) Score 260/300

March 2003, Athens, Greece

German (basic)

COMPUTER SKILLS

MS Office, EvoRad, eFilm-Medical

INTERESTS

Tennis, Padel tennis, Martial Arts

Abstract

Introduction

Lower extremity artery disease (LEAD) is a common disease leading to pronounced morbidity and mortality as well as to consumption of many health-care and social-care resources. Major risk factors include ageing population, increasing prevalence of diabetes and its lower-limb-related complications, along with tobacco consumption. Critical limb ischemia (CLI), the most severe clinical manifestation of LEAD, may present with ischemic foot ulcers, rest pain, and gangrene.

Ischemic ulcers often begin as minor traumatic wounds that subsequently fail to heal because the blood supply is insufficient to meet the increased demands of the healing tissue. Furthermore, ischemic ulceration is potentially associated with increased risk for subsequent limb loss, high healthcare costs and mortality.

Therefore, the aim of our study was first to evaluate the technical effectiveness of PTA in the management of lower limb atheromatous lesions in patients with ischemic foot ulceration in a real-life setting. The secondary aim was to assess the clinical effectiveness of PTA, including ulcer healing and amputation-free survival in these patients.

Materials and methods

Study Population

We conducted a single-center, prospective cohort, observational study which included patients presenting with ischemic foot ulcers between June

2009 and June 2015. Inclusion criteria were an ulcer in the foot and an ankle-brachial index (ABI) <0.9 or toe-brachial index (TBI) <0.7, in case of incompressible tibial arteries at the level of the ankle. The exclusion criteria were: refusal to participate, refusal of percutaneous transluminal angioplasty (PTA) therapy, absolute contraindication to contrast media injection as determined by the investigator, uncontrollable coagulopathy, unwilling or unable to provide informed consent or return for required follow-up evaluations. Revascularization was performed by endovascular means whenever feasible after an initial evaluation of all patients. Furthermore, cases in which surgical revacularization was considered as first line treatment, were also excluded.

All patients provided written informed consent and ethical approval was granted by our Hospital Ethics Committee.

If non-invasive parameters suggested LEAD, we performed CT angiography or Digital Subtraction Angiography (DSA). andarranged the endovascular procedure based on angiographic findings In cases where a diagnostic DSA was done, endovascular revascularization was performed during the same session when feasible. Evaluation of short-term and long-term clinical success of the procedure was based on ulcer size and appearance.

Technique

The main goal of the angioplasty (defining technical success) was to achieve straight-line flow (SLF) from the aorta down to either a patent dorsalis pedis or distal posterior tibial artery supplying the plantar arch. The definition of technical success also included creation of SLF from the

aorta to a peroneal artery that supplies either a patent dorsalis pedis or distal posterior tibial via collateral reconstitution.

All patients received PTA-first as the primary form of treatment. They also received medical therapy for risk factor modification. Hypertension definition In a subgroup of patients, autologous platelet-rich plasma (PRP) was used with the results published elsewhere.

All angioplasties were performed by two interventional radiologists of our department who had 1 and 10 years of expierience, at the beginning of the study.

Our typical angioplasty strategy was to attempt intraluminal crossing of the stenoses or occlusions using a combination of a 5F curved catheter and a 0.035 in. straight or curved hydrophilic guidewire (Terumo). In case a subintimal channel was created, we switched our technique and attempted subintimal angioplasty. To facilitate intraluminal crossing of chronic total occlusions, we also used Vibrational angioplasty in a subcohort of our patients (18).

Technical success of the endovascular procedure was accomplished when a residual stenosis less than 30% was achieved with antegrade blood flow in at least one distal vessel. Adverse events were classified according to the Society for Vascular

Follow-up

The study was designed to follow up patients for at least 2 years. However, follow-

Post-procedure surveillance included quarterly vascular clinic visits, during which clinical improvement (e.g. wound healing, rest pain) was assessed. Follow-up was

Results

Patients

A total of 225 patients with ischemic foot ulceration were initially evaluated during the study period. Among those, 12 patients were excluded due to various contra-indications for endovascular treatment. From the 213 remaining cases, 52 patients had a profoundly unfavourable distribution of lesions for an endovascular approach, according to the vascular team's consensus, leaving 161 (76%) patients that underwent percutaneous procedures. Moreover, 17 patients were lost to follow-up before reaching any of the study endpoints. Finally, 144 patients were studied, 102 of whom (71%) were followed-up for more than 24 months.

PTA was performed in all 144 patients . Lesion type incidence according to TASC II classification was 10 Type A, 19 Type B, 72 Type C, and 43 Type D. In 88 patients PTA was performed in the iliofemoral axis exclusively, in 10 patients in the popliteal/tibial axis exclusively, and in 46 in both levels, with an average of 1.8 procedures per patient. One vessel was treated in 66 cases two vessels in 45 cases,three vessels in 22 casesand four vessels in 11 cases . Stent placements were required in 42 cases. Initial technical success was achieved in 141 cases . Technical success by type of lesion was 100% for Type A and B lesions, 98% for

Type C and 95% for Type D lesions. The ABI significantly increased post-procedurally from 0.45 ± 0.2 to 0.76 ± 0.19, p<0.001.

Complications

Adverse clinical events occurred in 13 patients. One patient

Vascular re-interventions

Repeat PTA to the initially recanalized artery was performed in 8 patients during the follow-up period.

Amputations

Despite successful recanalization, minor or major amputation was required in 36 cases. Of these, 17 were major and 19 minor amputations. The need for amputation was correlated with the extent of tissue destruction at inclusion (r=0.3, p=0.039).

Ulcer healing

In total, 98 (68%**)** patients healed primarily without major or minor amputation. Median time to healing was 18 weeks (3-52 weeks).

Survival

At a mean follow-up of 3.1 ± 1.8 years the survival rate was 69% (44 patients died, 28 of whom from cardiac causes, 8 from stroke, 4 from uncontrolled sepsis and 4 from malignancy).

Amputation-free survival: During the follow-up period, amputation-free survival was 64%.

Amputation-free survival with healed ulcers: During the follow-up period, 62% of patients had achieved ulcer healing and were alive without a major or minor amputation.

Discussion

Our data support the technical and clinical success of PTA in the management of ischemic foot ulcers with high rates of healing and limb salvage. PTA was technically successful and feasible in almost all patients with only a minority of cases unsuitable for percutaneous techniques due to extensive and complex distribution of atherosclerotic lesions.

Another important aspect of our study is that most of the patients' lesions were classified as TASC II Type C and D, with 98% and 95% technical success respectively, indicating that endovascular procedures can be performed in patients to whom surgical intervention was previously recommended. Therefore, our results

In conclusion, endovascular intervention as first-line treatment in subjects with arterial insufficiency and ischemic foot ulcers is feasible in the vast majority of patients, and has a very high technical success rate. Percutaneous revascularization results in a high overall incidence of wound healing and limb salvage, accompanied by very low morbidity and mortality rates. Factors that affect clinical success, potentially affecting optimal treatment strategy are the extent of tissue destruction at presentation, along with patient comorbidities.

Abstract in Greek

Περίληψη στα ελληνικά

Εισαγωγή

Η Αρτηριακή Νόσος των Κάτω Άκρων (ΑΝΚΑ) είναι μία συνήθης νόσος που οδηγεί σε αυξημένη νοσηρότητα και θνητότητα, καθώς και κατανάλωση πολλαπλών πόρων του συστήματος υγείας και κοινωνικής φροντίδας. Κύριοι παράγοντες κινδύνου αποτελούν η γήρανση του πληθυσμού, η αυξημένη επίπτωση του διαβήτη και των επιπλοκών του στα κάτω άκρα, σε συνδυασμό με την κατανάλωση καπνού. Η Κρίσιμη Ισχαιμία των Άκρων (ΚΙΑ), η σοβαρότερη κλινική εκδήλωση της ΑΝΚΑ, δύναται να εκδηλωθεί ως ισχαιμικό έλκος, άλγος ηρεμίας ή γάγγραινα.

Τα ισχαιμικά έλκη ενίοτε ξεκινούν ως ελάσσονες τραυματισμοί που εν συνεχεία δεν επουλώνονται επειδή η αιμάτωση δεν επαρκεί για τις αυξημένες ανάγκες επούλωσης των ιστών. Επιπλέον, τα ισχαιμικά έλκη ενδέχεται να σχετίζονται με αυξημένο κίνδυνο απώλειας του μέλους, αύξηση του κόστους περίθαλψης και της θνητότητας.

Συνεπώς σκοπός της μελέτης μας ήταν κατά πρώτο λόγο, η εκτίμηση της αποτελεσματικότητας της διαδερμικής αγγειοπλαστικής στην αντιμετώπιση των αθηρωματικών βλαβών σε ασθενείς με ισχαιμικά έλκη κάτω άκρων, σε ρεαλιστικό υπόβαθρο. Κατά δεύτερο λόγο, σκοπός μας ήταν η εκτίμηση της κλινικής αποτελεσματικότητας της αγγειοπλαστικής, συμπεριλαμβανομένης της επούλωσης των ελκών και της επιβίωσης άνευ ακρωτηριασμού στην συγκεκριμένη ομάδα ασθενών.

Υλικό και μέθοδος

Πληθυσμός μελέτης

Πραγματοποιήθηκε μία μονοκεντρική προοπτική μελέτη παρατήρησης, στην οποία συμπεριελήφθησαν οι ασθενείς που παρουσίασαν ισχαιμικά έλκη κάτω άκρων την περίοδο μεταξύ Ιουνίου 2009 και Ιουνίου 2015. Κριτήρια επιλογής ήταν Σφυροβραχιόνιος Δείκτης (ΣΒΔ) <0,9 ή Δακτυλοβραχιόνιος Δείκτης (ΔΒΔ) <0,7, σε περίπτωση ασυμπίεστων κνημιαίων αγγείων στα σφυρά. Κριτήρια αποκλεισμού ήταν: άρνηση συμμετοχής, άρνηση ενδαγγειακής θεραπείας, απόλυτη αντένδειξη για χρήση ενδοφλεβίου σκιαγραφικού κατά την κρίση του ερευνητή, μη-ελεγχόμενο πρόβλημα πήξεως, άρνηση ή αδυναμία συγκατάθεσης ή επανόδου για επανεξέταση. Η επαναγγείωση πραγματοποιήθηκε ενδαγγειακά όποτε ήταν δυνατόν, κατόπιν της αρχικής εκτίμησης σε όλους τους ασθενείς. Επιπρόσθετα, αποκλείσθηκαν επίσης οι ασθενείς στους οποίους η χειρουργική επαναγγείωση θεωρήθηκε πρώτης γραμμής θεραπεία.

Όλοι οι ασθενείς προσέφεραν έγγραφη συγκατάθεση κατόπιν ενημέρωσης, ενώ εδόθη και η έγκριση της Επιτροπής Ηθικής του νοσοκομείου μας.

Εάν οι αναίμακτες μέθοδοι ήταν δηλωτικές ΑΝΚΑ, πραγματοποιήθηκε ΥΤ-αγγειογραφία ή Ψηφιακή Αφαιρετική Αγγειογραφία (ΨΑΑ) και η ενδαγγειακή θεραπεία προγραμματίστηκε με βάση τα αγγειογραφικά ευρήματα. Σε περίπτωση πραγματοποίησης διαγνωστικής ΨΑΑ, η ενδαγγειακή επαναγγείωση έγινε εάν ήταν εφικτό στην ίδια συνεδρία. Η

εκτίμηση της βραχυπρόθεσμης και μακροπρόθεσμης κλινικής επιτυχίας βασίστηκε στο μέγεθος και την εμφάνιση των ελκών.

Τεχνική

Ο κύριος στόχος της αγγειοπλαστικής (ορισμός της κλινικής επιτυχίας) ήταν να επιτευχθεί ροή σε ευθεία γραμμή (ΡΕΓ) από την αορτή έως μία βατή ραχιαία του ποδός αρτηρία ή περιφερική οπίσθια κνημιαία αρτηρία που αρδεύει το πελματιαίο τόξο. Ο ορισμός της τεχνικής επιτυχίας περιελάμβανε επίσης δημιουργία ΡΕΓ από την αορτή στην περονιαία αρτηρία η οποία αρδεύει μία βατή ραχιαία του ποδός ή οπίσθια κνημιαία μέσω παραπλεύρου δικτύου. Όλοι οι ασθενείς έλαβαν ενδαγγειακή αντιμετώπιση ως πρώτη θεραπεία. Επίσης εδόθη θεραπεία τροποποίησης παραγόντων κινδύνου. Σε μία υποομάδα ασθενών χρησιμοποιήθηκε αυτόλογο πλάσμα πλούσιο σε αιμοπετάλια (ΠΠΑ) με δημοσιευμένα αποτελέσματα.

Οι αγγειοπλαστικές πραγματοποιήθηκαν από δύο Επεμβατικούς Ακτινολόγους του τμήματός μας που είχαν 1 και 10 έτη εμπειρίας κατά την έναρξη της μελέτης. Η τυπική στρατηγική της αγγειοπλαστικής ήταν η προσπάθεια ενδοαυλικής διάνοιξης των στενώσεων ή αποφράξεων χρησιμοποιώντας έναν συνδυασμό κυρτού καθετήρα 5F και ενός κυρτού ή ευθέως υδρόφιλου οδηγού σύρματος 0,035 ιν. (Terumo). Σε περίπτωση δημιουργίας υπενδοθηλιακού διαύλου, η τεχνική τροποποιείτο και γίνοταν προσπάθεια υπενδοθηλιακής αγγειοπλαστικής. Για να επιτύχουμε ενδοαυλική διάνοιξη σε χρόνιες πλήρεις αποφράξεις χρησιμοποιήσαμε επίσης Αγγειοπλαστική Δονήσεων σε μία οποομάδα των ασθενών μας. Τεχνική επιτυχία της ενδαγγειακής μεθόδου θεωρήθηκε η παρουσία

υπολοιπόμενης στένωσης κάτω του 30% με ορθόδρομη ροή σε τουλάχιστον ένα περιφερικό αγγείο.

Παρακολούθηση

Η μελέτη σχεδιάστηκε με στόχο την παρακολούθηση των ασθενών επί τουλάχιστον 2 έτη. Η παρακολούθηση συνίστατο σε τριμηνιαία επίσκεψη στα εξωτερικά ιατρεία στην οποία γινόταν εκτίμηση της κλινικής βελτίωσης (π.χ. επούλωσης ελκών, άλγους ηρεμίας).

Αποτελέσματα

Ασθενείς

Κατά την διάρκεια της περιόδου της μελέτης εξετάσθηκαν 225 ασθενείς με ισχαιμικά έλκη κάτω άκρων. Από αυτούς, 12 ασθενείς αποκλείσθηκαν λόγω διαφόρων αντενδείξεων ενδαγγειακής θεραπείας. Από τους υπόλοιπους 213 ασθενείς, οι 52 είχαν εξαιρετικά απρόσφορη κατανομή, βλαβών για ενδαγγειακή θεραπεία, κατά την εκτίμηση της θεραπευτικής ομάδας, αφήνοντας 161 ασθενείς (76%) οι οποίοι ακολούθησαν ενδαγγειακή θεραπεία. επιπλέον, 17 ασθενείς δεν εμφανίστηκαν στους επανελέγχους και δεν έφθασαν κάποιο τελικό σημείο της μελέτης. Τελικά, 144 ασθενείς μελετήθηκαν, οι 102 εκ των οποίων (71%) παρακολουθήθηκαν για πάνω από 24 μήνες.

Αγγειοπλαστική πραγματοποιήθηκε και στους 24 ασθενείς. Ο τύπος των βλαβών σύμφωνα με την ταξινόμηση TASC II ήταν 10 τύπου A, 19 τύπου B, 72 τύπου C και 43 τύπου D. Σε 88 ασθενείς πραγματοποιήθηκε αγγειοπλαστική στον λαγονομηριαίο άξονα μόνο, σε 10 ασθενείς στον ιγνυακό/κνημιαίο άξονα μόνο και σε 46 και στα δύο επίπεδα, με μέσο όρο

1,8 επεμβάσεις ανά ασθενή. Ένα αγγείο αντιμετωπίστηκε σε 66 περιπτώσεις, δύο αγγεία σε 45 περιπτώσεις, τρία αγγεία σε 22 περιπτώσεις και τέσσερα αγγεία σε 11 περιπτώσεις. Τοποθέτηση stent ήταν απαραίτητη σε 42 περιπτώσεις. Αρχική εχνική επιτυχία επετεύχθει σε 141 περιτπωσεις. Η τεχνική επιτυχία ανάλογα με τον τύπο της βλάβης ήταν 100% για τύπου Α και Β, 98% για τύπου C και 95% για τύπου D. Ο ΣΒΔ αυξήθηκε σημαντικά μετά την επέμβαση από 0,45 ± 0,2 σε 0,76 ± 0,19, p<0,001.

Επιπλοκές

Ανεπιθύμητα συμβάματα παρατηρήθηκαν σε 13 ασθενείς.

Αγγειακές επανεπεμβάσεις

Επαναληπτική αγγειοπλαστική στις διανοιχθήσες αρτηρίες πραγματοποιήθηκε σε 8 ασθενείς κατά την διάρκεια της πέριόδου παρακολούθησης.

Ακρωτηριασμοί

Παρά τις επιτυχείς επαναγγειώσεις, σε 36 περιπτώσεις απαιτήθηκε μείζων ή έλλασσων ακρωτηριασμός. Από αυτούς, οι 17 ήταν μείζονες και οι 19 ελλάσσονες ακρωτηριασμοί. Η ανάγκαιότητα ακρωτηριασμού συσχετίσθηκε με την αρχική έκταση ιστικής καταστροφής (r=0,3, p=0,039).

Επούλωση ελκών

Συνολικά, 98 (68%) των ασθενών παρουσίασαν πρωτογενή επούλωση, δίχως ελλάσσονα ή μείζονα ακρωτηριασμό. Ο διάμεσος χρόνος επούλωσης ήταν 18 εβδομάδες (3-52 εβδομάδες).

Επιβίωση

Κατά τη διάρκεια μίας μέσης παρακολούθησης 3,1 ± 1,8 ετών, η επιβίωση ήταν 69% (44 ασθενείς απεβίωσαν, 28 από καρδιακά αίτια, 8 από αγγειακό εγκεφαλικό επεισόδιο, 4 από ανεξέλεγκτη σήψη και 4 από κακοήθεια).

Επιβίωση άνευ ακρωτηριασμού: Κατά την διάρκεια της περιόδου παρακολούθησης η επιβίωση άνευ ακρωτηριασμού ήταν 64%.

Επιβίωση άνευ ακρωτηριασμού με επούλωση ελκών: Κατά την διάρκεια της περιόδου παρακολούθησης 62% των ασθενών παρουσίασαν επούλωση ελκών και ήταν εν ζωή χωρίς μείζονα ή ελλάσσονα ακρωτηριασμό.

Συζήτηση

Τα δεδομένα μας υποστηρίζουν την τεχνική και κλινική επιτυχία της αγγειοπλαστικής στην αντιμετώπιση των ισχαιμικών ελκών των κάτω άκρων, με υψηλά ποσοστά επιτυχίας και διάσωσης μέλους. Η αγγειοπλαστική ήταν τεχνικά επιτυχής και πρόσφορη σε σχεδόν όλους τους ασθενείς με μόνο μία μειονότητα περιπτώσεων απρόσφορη για διαδερμικές τεχνικές λόγω εκτεταμένης και πολύπλοκης κατανομής αθηρωματικών αλλοιώσεων. Μία άλλη σημαντική πτυχή της μελέτης μας ήταν ότι οι περισσότερες βλάβες των ασθενών μας ταξινομήθηκαν ως TASC II τύπου C και D, με 98% και 95% τεχνική επιτυχία αντίστοιχα, ενδεικτικό ότι οι ενδαγγειακές τεχνικές δύναται να πραγματοποιηθούν σε ασθενείς στους οποίους παλαιότερα συνιστάτο χειρουργική θεραπεία.

Συμπερασματικά, οι ενδαγγειακές επεμβάσεις είναι δυνατόν να πραγματοποιηθούν στην συντριπτική πλειοψηφία των ασθενών με

αρτηριακή ανεπάρκεια και ισχαιμικά έλκη κάτω άκρων και έχουν πολύ υψηλή τεχνική επιτυχία. Η διαδερμική επαναγγείωση έχει ως αποτέλεσμα υψηλά ποσοστά επούλωσης ελκών και διάσωσης μέλους, σε συνδυασμό με πολύ χαμηλά ποσοστά νοσηρότητας και θνητότητας. Παράγοντες που επηρρεάζουν την κλινική επιτυχία και πιθανώς την βέλτιστη θεραπεία είναι η αρχική έκταση ιστικής βλάβης, καθώς και οι συνοσηρότητες.

PART I

PAD: Principles of Diagnosis and Management

Chapter 1

Lower extremity peripheral artery disease

Introduction

Atherosclerosis is the result of lipid and fibrous material accumulation in the arterial wall causing disease of the coronaries, cerebral, and peripheral arteries. It cause of acute or chronic symptoms due to embolism from more proximal disease, or due to total occlusion of an artery. Atherosclerotic disease involving the arteries of the lower extremities is referred as lower extremity peripheral artery disease (PAD).

Anatomy and pathophysiology

The subintimal accumulation of lipid and fibrous material (ie, plaque) is able to create stenoses of the vessel lumen, with subsequent thrombosis, or the plaque can rupture, resulting in occlusion of downstream vessels. Many factors contribute to atherosclerosis pathogenesis, such as endothelial dysfunction, dyslipidemia, inflammatory and immunologic factors, and tobacco use. The symptoms related to atherosclerotic stenoses of the aorta or lower extremity arteries depend upon the location and severity of disease. In any arterial segment (aortoiliac, femoropopliteal, tibial), the plaque tends to occur in proximally or in the mid-segment (eg, proximal bifurcation leading to that vascular bed). Atherosclerotic disease develops in anatomic patterns, which also have a bearing on the natural history and progression of disease. Patients suffering from diabetes or with end-stage renal disease generally present with more distal disease.

Atherosclerosis in the aorta can coexist with aneurysm formation. The pathology of aneurysmal disease is considered distinct from that of atherosclerosis; however, the clinical manifestations may overlap.

Epidemiology and risk factors

The overall prevalence of lower extremity PAD varies extensively depending upon the population studied but is estimated to be approximately 10 percent of adults older than 55 years [1]. Data from the 2010 United States census indicate that the overall burden of PAD among adults in the United States is greater for women compared with men [2]. Well-defined risk factors are linked to the development of PAD and include older age, hypertension, tobacco use, diabetes, and hypercholesterolemia, among others [3-5].

Clinical presentations

The clinical manifestations of PAD (claudication, rest pain, ulceration, and gangrene) are predominantly the result of progressive luminal narrowing (stenosis/occlusion), although thrombosis or embolism of unstable atherosclerotic plaque or thrombotic material can also occur [6]. The natural history of patients who present with mild-to-moderate claudication is generally benign, which contrasts with the more aggressive presentation seen in those who present with ischemic rest pain or ulceration. Single-level atherosclerotic disease (ie, aortoiliac, superficial femoral) often manifests initially as claudication. Multilevel disease can also manifest as claudication when collateral circulation is adequate, but often presents as ischemic rest pain or lower extremity ulceration when a well-developed collateral circulation is absent. Severe clinical presentations can develop without an intervening history of claudication, particularly in older patients with diabetes or chronic kidney disease.

Evidence of underlying atherosclerotic occlusive disease may be present in the absence of clinical symptoms. It is estimated that there are three times as many asymptomatic patients with lower extremity PAD as there are patients with symptoms [7]. Although patients with

asymptomatic PAD may not report exertional leg discomfort by definition (ie, claudication), lower extremity physiological function may be impaired compared with matched controls without PAD [8].

The most prevalent form of atherosclerotic disease among asymptomatic patients is atherosclerosis of the iliac and femoral arteries [9]. Due to the fact that the presence of PAD may predict the risk for future cardiovascular events, screening for PAD in asymptomatic high-risk individuals using the anklebrachial index (ABI) is advocated by some, but not all expert groups [10-15]. In the Viborg Vascular (VIVA) screening trial, 50,156 men aged 65 to 74 years were randomly assigned to screening versus no screening for the presence of hypertension, PAD, and abdominal aortic aneurysm. After a median 4.4 years of follow-up, a small, but significant mortality benefit was noted, likely due to adoption of preventive strategies in the screened group [10].

Intermitent Claudication

Exertional discomfort in patients with lower extremity PAD is termed "claudication," which is derived from the Latin word "claudico" (to limp). Claudication is a reproducible symptom of a defined group of muscles that is induced by exercise and relieved with rest. Claudication can present unilaterally or bilaterally, as buttock and hip, thigh, calf, or foot pain, isolated or in combination. The severity of symptoms depends upon the number and degree of arterial stenoses, the collateral circulation, and the vigor of extremity use.

Chronic limb-threatening ischemia

Chronic limb-threatening ischemia (CLTI) is a clinical syndrome defined by the presence of PAD followed by rest pain, gangrene, or a lower limb ulceration >2 weeks duration. CLTI is the preferred term replacing the previous terms of critical limb ischemia (CLI) or severe limb ischemia [16]. The use of the term CLTI manifests changes in arterial disease patterns and the concept that CLTI is a spectrum of disease. The nature of the specific clinical manifestations depends

upon the time course over which arterial narrowing or occlusion occurs; this in turn affects the extent to which the collateral circulation can develop. Acute-on-chronic reductions in limb perfusion, often due to atheroembolism, cholesterol embolism, or thrombotic occlusion of a stenotic vessel, cause diffuse limb pain [1]. Chronic severe lowering in limb perfusion present as ischemic rest pain typically localized to the forefoot and toes, or as tissue loss (nonhealing ulcer, gangrene).

Diagnosis

In patients with a relevant history and physical examination findings, the diagnosis of PAD is established with the measurement of an ankle-brachial index (ABI) ≤0.9. The ABI is a ratio of the resting systolic blood pressure at the ankle to the higher systolic brachial pressure. For patients with appropriate symptoms, but a normal ABI, we obtain an ABI following exercise. Duplex ultrasonography is commonly used in combination with the ABI to identify the location and severity of arterial obstruction [17]. Advanced vascular imaging methods (computed tomographic [CT] angiography, magnetic resonance [MR] angiography, catheter-based arteriography) are usually reserved for patients in whom there remains uncertainty following noninvasive testing, or in whom intervention is anticipated [18,19].

Classification

Classification of lower extremity PAD, by grading symptoms and the anatomic lesions responsible for these symptoms, provides an objective measure by which to follow patients clinically, and insures consistency when comparing medical and interventional treatment strategies in clinical studies.

Claudication is defined functionally by the initial and absolute walking distance and on the Society of Vascular Surgery Rutherford scale graded from 1 to 3 (Table 1). Atherosclerotic manifestations of disease in the lower extremities are classified by TASCII criteria according to their anatomic distribution, multiplicity of lesions, and the nature of the lesion (stenosis or occlusion) [20].

The Global Vascular Guidelines for the management of chronic limb-threatening ischemia recommend staging the limb using the Society for Vascular Surgery (SVS) lower extremity threatened limb classification system, WIfI (Wound, Infection, foot Infection) (Table 2) [16]. WIfI classifies the severity of limb threat in a manner that is intended to more accurately reflect important clinical considerations that impact management and amputation risk (figure 2) [21,22]. WIfI restaging can also be used to help to assess the adequacy of intervention [21].

GLASS – The Global Anatomic Staging System (GLASS) is an anatomic classification (table 3) that grades the level of disease in the femoropopliteal and infrapopliteal segments of the preferred target artery path [16]. These are combined to provide an overall grade of complexity for lower extremity interventions.

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Chapter 2

Leg ulcers- Differential diagnosis

INTRODUCTION

Leg ulcers are an increasing problem worldwide and represent a major health care burden [1]. Patients with leg ulcers are managed by clinicians in multiple specialties, including primary care, vascular surgery, plastic surgery, podiatry, wound care, and dermatology.

A leg ulcer is a physical finding that can result from multiple etiologies, rather than a diagnosis. Thus, determination of the cause is essential for selecting appropriate treatment and determining the need for further evaluation. The most common causes of leg ulcers are venous insufficiency, arterial insufficiency, and neuropathic disease.

DEFINITION

The term "ulcer" describes destruction of the epidermis that extends into the dermis and may reach subcutaneous fat or deeper tissues.

COMMON CAUSES

Venous, arterial, and neuropathic ulcers account for up to 90 percent of leg ulcers. In a survey study in which wound care professionals in Germany reported the etiologies of chronic leg ulcers in over 31,000 patients, venous insufficiency, arterial insufficiency, and mixed venous and arterial insufficiency accounted for 48, 15, and 18 percent of chronic ulcers, respectively [2]. Ulcers caused by a combination of venous insufficiency and peripheral arterial disease (PAD) are increasingly diagnosed, an observation related to the increasing incidence of atherosclerosis and obesity.

Venous insufficiency

Chronic venous disease is the most common cause of leg ulcers. Examples of risk factors include advancing age, female sex, obesity,

pregnancy, prolonged standing, and a history of deep venous thrombosis.

Clinical features: Venous insufficiency ulcers frequently affect the "gaiter" area of the leg, which extends from the mid-calf to ankle. The skin immediately above the medial or lateral malleolus is the most common site, with the medial aspect affected most frequently. Ulcers are typically shallow with irregular borders with yellow, fibrinous exudate overlying the wound bed. Pain is mild to moderate. Arterial pulses are normal unless there is concomitant arterial insufficiency.

Additional clinical findings in chronic venous disease include telangiectasias of the feet and ankles, peripheral edema, venous varicosities, and brown discoloration of the lower legs and feet due to hemosiderin deposition in tissue macrophages.

Venous stasis dermatitis characterized by erythema and scaling may develop around ulcers. Lipodermatosclerosis, also known as sclerosing panniculitis, may develop in the setting of long-standing venous hypertension and insufficiency. Lipodermatosclerosis presents as induration and fibrosis of the lower medial leg, which may be erythematous and painful and mistaken for cellulitis.

Diagnosis: Venous ulcers are diagnosed by clinical examination. Noninvasive venous imaging with duplex ultrasonography assesses reflux and obstruction in the superficial, deep, and perforating veins and is indicated if the diagnosis is not clear or if surgical intervention is being considered.

Arterial insufficiency

Peripheral arterial disease (PAD), a manifestation of atherosclerosis, leads to reduced blood flow to the extremities and may result in tissue necrosis and leg ulcers. Examples of risk factors for PAD include

diabetes, smoking, hypertension, and hyperlipidemia [3]. Patients may have a history of myocardial infarction, angina, or stroke.

Clinical features: Arterial insufficiency (ischemic) ulcers typically occur distally on the toes or on pressure areas, such as the heel, malleoli, and shin. Ulcers have well-demarcated edges, giving them a "punched-out" appearance, often with an overlying necrotic eschar. Unlike venous ulcers, arterial ulcers typically are very painful.

Patients with PAD may complain of intermittent claudication or, later, rest pain. On examination, decreased hair density, shiny and thin skin, diminished or absent peripheral pulses, or prolonged capillary refill time (>3 to 4 seconds) may be present. Prolonged pallor with leg elevation to 45° for 1 minute (Buerger's test) supports vascular compromise. Peripheral dry gangrene may occur with disease progression.

Diagnosis: Peripheral arterial disease should be confirmed with ankle-brachial index (ABI) testing.

Neuropathy

Diabetic neuropathy is responsible for the vast majority of neuropathic ulcers. Diabetic patients may have up to a 25 percent lifetime risk of developing a foot ulcer. Other causes of peripheral neuropathy (eg, spinal cord disorders [injury or spina bifida], tabes dorsalis, alcohol abuse, nutritional deficiencies, and autoimmune diseases) may result in similar ulcerations.

Clinical features: Neuropathic ulcers are painless and occur over pressure points on the foot or heel. Ulcers have a punched-out morphology and typically occur within a thick callus. Associated clinical findings of diabetic neuropathy include claw toes, neuropathic (Charcot) arthropathy, and reduced sweating resulting in dry, scaly feet.

Diagnosis: Sensory examination confirms decreased sensation in the involved areas. Ulcers can become deep, and underlying osteomyelitis should be considered when ulcers do not heal with off-loading therapies.

LESS COMMON CAUSES

There are multiple less common causes of leg ulcers, including physical injury, infection, vasculopathy, pyoderma gangrenosum (PG), panniculitis, malignancy, medications, and brown-recluse spider envenomation.

Physical injury

Physical injury to the skin may cause ulceration. Ulcers may result from pressure, thermal injury (burns or cold injury), radiation exposure, iatrogenic injury, or factitial (self-induced) injury. Of note, traumatic ulcers on the lower legs can demonstrate prolonged healing in older individuals and patients with underlying venous hypertension or arterial insufficiency.

Clinical features: Ulcer features vary depending on the inciting injury. In particular, pressure ulcers often occur in sites overlying bony prominences; on the lower extremity, the heels are common sites [4]. The appearance of pressure ulcers ranges from shallow open ulcers to deep ulcers that expose bone, tendon, or muscle.

Diagnosis: With the exception of factitial ulcers, diagnosis is largely straightforward and relies on historical evidence of skin trauma.

Infection

Primary infectious ulcers may result from bacterial, fungal, spirochete, or protozoal infections, either by direct inoculation or systemic spread.

Staphylococcal and streptococcal skin infections are common bacterial infections that may result in ulceration. Cutaneous ulcers also may result from atypical mycobacterial infections, late-stage syphilis (gummas), deep fungal infections (eg, coccidioidomycosis,

blastomycosis, histoplasmosis), and protozoal infections (eg, leishmaniasis). These infections most commonly, but not exclusively, occur in immunosuppressed patients.

Clinical features: Clinical features vary according to the type of infection. Furuncles secondary to methicillin-resistant Staphylococcus aureus (MRSA) may progress to form larger abscesses, cellulitis, or ulcerative, necrotic plaques. Ecthyma, a form of nonbullous impetigo caused by Streptococcus pyogenes (with frequent contamination with S. aureus), produces punched-out shallow ulcers with a purulent necrotic crust and surrounding erythema. Ecthyma gangrenosum, a Pseudomonas aeruginosa infection characterized by bacterial invasion of the media and adventitia of arteries and veins, results in the rapid development of gangrenous ulcers with black eschar. Ecthyma gangrenosum usually occurs in immunocompromised patients.

Diagnosis: The diagnosis of infectious ulcers requires identification of the causative organism via swab cultures for aerobic bacteria or tissue culture for bacteria, fungi, and atypical mycobacteria. For tissue culture, incisional or punch biopsies should be obtained from the edge of the ulcer, placed on a sterile gauze pad moistened with non-bacteriostatic saline, and sent for culture in a sterile urine cup. In addition, ulcer edge tissue should be sent for histopathologic examination, including special stains for infectious organisms, since this may yield a more rapid diagnosis than culture. Culture can take up to six weeks for certain mycobacteria and fungi.

In addition, secondary bacterial infection can complicate chronic ulcers caused by venous insufficiency, arterial insufficiency, neuropathic disease, or other etiologies. Clinical signs such as exacerbations of erythema, warmth, edema, and exudate warrant investigation for secondary infection.

Vasculopathy

Vasculopathic disorders can cause lower extremity ulcers by means of inflammatory processes that cause destruction of blood vessel walls (vasculitis) or vessel occlusion leading to ischemia.

Vasculitis

Vasculitis of small or medium-sized cutaneous blood vessels can result in leg ulcers. Small-vessel vasculitis can be idiopathic or a consequence of infections, drugs, mixed cryoglobulinemia, autoimmune disorders (eg, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome), or malignancies (particularly hematologic malignancies). Inflammation of both small and medium-sized cutaneous blood vessels is associated with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, including granulomatosis with polyangiitis (formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), and microscopic polyangiitis. Inflammation of medium-sized blood vessels occurs in cutaneous and systemic polyarteritis nodosa.

Clinical features: The characteristic clinical finding of cutaneous small-vessel vasculitis is palpable purpura. Palpable purpura may develop an overlying necrotic vesicle or bulla that becomes ulcerative. Subcutaneous nodules, necrotic ulcerations, retiform purpura, and livedo racemosa are features of medium-sized vessel involvement.

Diagnosis: A diagnosis of vasculitis requires a skin biopsy that reaches the subcutis. In cutaneous small-vessel vasculitis, biopsy of an early but palpable lesion is most informative [5]. Biopsies demonstrate leukocytoclastic vasculitis (infiltration of postcapillary venules by neutrophils undergoing degranulation and fragmentation) and fibrinoid necrosis of the involved vessels. Similar changes occur in vasculitis of medium-sized vessels involving the small arteries in the deep reticular dermis and fat. Performance of direct immunofluorescence

studies to identify immunoglobulin or complement deposits is an important component of the evaluation of cutaneous vasculitis.

Livedoid vasculopathy

Livedoid vasculopathy (LV) is a chronic, painful, ulcerative skin condition, most common in young and middle-aged women [6]. While the pathogenesis of LV is not clearly understood, hypercoagulable states and impaired fibrinolysis have been implicated [7].

Clinical features: LV is characterized by crusted, painful, stellate, shallow ulcerations that are slow to heal. The disease is often bilateral, involving the skin around the ankle and dorsal foot. The ulcers heal with white, atrophic, stellate scars with telangiectasia, known as atrophie blanche. The terms atrophie blanche and livedoid vasculopathy have been used interchangeably in older literature; however, atrophie blanche is now recognized as a healing pattern that can occur as a result of both LV and chronic venous insufficiency.

Diagnosis: A skin biopsy is used to confirm the diagnosis. Characteristic findings are hyaline thrombi in the mid and upper dermal blood vessels with fibrinoid changes in vessel walls. Further evaluation for hypercoagulable states, paraproteinemias, cryoprecipitable proteins (cryoglobulins or cryofibrinogen), and collagen vascular disease may be helpful as indicated by history and physical examination.

Thromboangiitis obliterans

Thromboangiitis obliterans (TAO, Buerger's disease) is a vaso-occlusive inflammatory vasculopathy affecting small and medium-sized arteries, veins, and nerves of the extremities. The pathophysiology of TAO is characterized by inflammatory thrombi occluding vessels, with sparing of the vessel walls.

A rare disorder, TAO most commonly affects young to middle-aged male smokers. Exposure to tobacco is considered essential to initiation and progression of the disorder.

Clinical features: The legs are affected more often than the arms. Affected individuals present with ischemic symptoms of the extremities, which may progress to digital gangrene and ulcerations. Raynaud phenomenon and superficial thrombophlebitis are other common features [8].

Diagnosis: TAO is a clinical diagnosis requiring a compatible history (including tobacco use), physical findings, and diagnostic changes on angiography. Angiography demonstrates involvement of the small and medium-sized arteries, segmental occlusions, and "corkscrew"-shaped collateral vessels around areas of occlusion.

Microvascular occlusion disorders

Occlusion of small cutaneous blood vessels may occur by multiple mechanisms, such as platelet plugging (eg, thrombocythemia, heparin-induced necrosis), cryoagglutination (eg, cryoglobulinemia, cryofibrinogenemia), bacterial infection (eg, ecthyma gangrenosum), embolism (eg, cholesterol emboli, oxalosis), coagulopathies (eg, antiphospholipid syndrome, protein C or S deficiency, warfarin necrosis), and calciphylaxis [9]. The clinical features vary with etiology. Overall, cutaneous ulcerations resulting from microvascular occlusion typically are very painful and retiform purpura are a common associated finding. The approach to diagnosis is also dependent on the etiology; histologic examination often is useful.

Examples of clinical and histologic findings of specific microvascular occlusion disorders include:

- **Cryoglobulinemia (type I) and cryofibrinogenemia:** Patients with type I cryoglobulinemia or cryofibrinogenemia may exhibit retiform

acral purpura or skin necrosis leading to ulceration. Involvement of other acral sites including ears and nose may also occur, especially with cryoglobulinemia. Livedo reticularis, the Raynaud phenomenon, and acral cyanosis are additional common clinical findings. Histopathologic examination of early sites of involvement reveals bland hyaline thrombi or red cell occlusion of superficial dermal blood vessels.

- **Cholesterol emboli:** An abrupt onset of widespread livedo reticularis plus distal retiform purpura is strongly suggestive of cholesterol emboli (more common) or oxalate emboli (rare). Peripheral gangrene and ulcerations occur in a subset of patients [10].

Cholesterol embolization is most common in men over age 50 with atherosclerotic disease. Cholesterol emboli may occur spontaneously, but are more commonly seen within hours to days of arterial catheterization. Thrombolytic therapy and starting anticoagulation therapy (warfarin blue toe syndrome) have also been implicated, but a causal relationship is not well established. Full-thickness punch or incisional biopsies to fat in sites of retiform purpura may demonstrate characteristic elongated clefts in deep dermal arterioles.

- **Oxalosis:** Oxalate embolism can occur in patients with primary hyperoxaluria. Patients develop hyperoxalemia and hyperoxaluria leading to recurrent urolithiasis that begins in childhood and subsequent progression to renal failure. Skin manifestations of oxalosis present after the onset of renal failure and include acrocyanosis, livedo reticularis, and cutaneous necrosis. Histopathologic examination reveals birefringent yellow-brown crystals within and around vessels in the deep dermis or fat.
- **Calciphylaxis:** Calciphylaxis, also referred to as calcific uremic arteriolopathy, presents with painful indurated reticulate purpuric plaques that progress to necrosis and ulceration. Calciphylaxis is most commonly seen in patients with renal failure, often in the setting of diabetes. Prognosis is poor [11].

Biopsies of involved skin must include the subcutaneous tissue; calcium deposits are found in the media of blood vessels in the fat.

Perieccrine calcium deposition may be a highly specific but not sensitive finding in calciphylaxis [12].

Sickle cell disease

Leg ulcers can occur as a complication of sickle cell disease. The ulcers most commonly occur on the medial and lateral malleoli and are usually painful and intractable [13,14]. The mechanism for ulcer development is not fully understood but may involve impaired blood flow, endothelial dysfunction, thrombosis, inflammation, and delayed healing [15].

Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis often associated with an underlying systemic disorder, such as inflammatory bowel disease, arthritis, or hematologic disease (eg, acute and chronic myelogenous leukemia, hairy cell leukemia, myelodysplasia, IgA monoclonal gammopathy) [16].

Clinical features: PG classically presents as single or multiple rapidly progressive painful leg ulcers with necrotic borders and surrounding erythema. The initial clinical finding is a pustule, which then develops an overlying necrotic bulla that ulcerates with purulent drainage. The lower leg is a common site of involvement [17]. PG may exhibit pathergy, the induction or worsening of PG in sites of trauma.

In its acute phase, PG may be accompanied by systemic symptoms or signs, such as fever and leukocytosis. In addition to the classic form, there are bullous, pustular, superficial granulomatous, and peristomal variants.

Diagnosis: PG is a diagnosis of exclusion, since there are no specific clinical, pathologic, or laboratory findings. Biopsies of an acute PG ulcer may demonstrate a neutrophilic infiltrate in the dermis, often with a surrounding mononuclear cell infiltrate.

Panniculitis

Panniculitides are disorders characterized by inflammation of the subcutaneous fat. Panniculitides associated with lower extremity ulcers include erythema induratum (nodular vasculitis) and panniculitis caused by alpha-1-antitrypsin deficiency or pancreatic disease.

Erythema induratum

Erythema induratum typically occurs in young or middle- aged women and involves the lower legs, especially the posterior calves. The disorder presents with tender subcutaneous nodules and plaques that may ulcerate and drain.

Biopsy demonstrates a mixed septal and lobular inflammatory cell infiltrate with vasculitis in most cases. Erythema induratum was classically described as a tuberculid associated with M. tuberculosis; however, erythema induratum may also be idiopathic or associated with other infections or drugs.

Alpha-1-antitrypsin deficiency

Alpha-1-antitrypsin deficiency produces a neutrophil panniculitis in a small subset of patients [18]. Patients develop tender erythematous or purpuric nodules and plaques on the lower trunk and extremities. The nodules and plaques may ulcerate, drain an oily discharge, and heal with scarring.

Biopsies of early alpha-1-antitrypsin deficiency panniculitis demonstrate a neutrophilic infiltrate of the fat followed by necrosis and destruction of fat lobules. Diagnosis is confirmed by serum evaluation of alpha-1-antitrypsin activity and genotype analysis.

Pancreatic panniculitis

Suppurative panniculitis is a rare complication of benign or malignant pancreatic disease [19]. Subcutaneous painful nodules develop on the lower extremities and trunk and may drain an oily material. Systemic symptoms may include fever, abdominal pain, and arthritis; ascites and pleural effusions may also be present.

Histopathologic examination of pancreatic panniculitis demonstrates septal and lobular inflammation, plus the diagnostic changes of fat necrosis and characteristic "ghost cells" and saponification of the fat.

Malignancy

Leg ulcers may arise as a feature of a primary cancer or as a result of malignant transformation of a chronic ulcer. Various cutaneous malignancies can cause ulcers. In a prospective study of 154 chronic leg ulcers in 144 patients that were diagnosed as venous ulcers but failed to respond to three months of standard treatment, biopsies revealed skin cancer in 16 ulcers (10 percent) [20]. Of the 16 malignant ulcers, there were 9 squamous cell carcinomas, 5 basal cell carcinomas, 1 melanoma, and 1 leiomyosarcoma. Cutaneous lymphomas (both B and T cell) and Kaposi's sarcoma may also cause leg ulcerations.

Malignant ulcers often are not recognized immediately. Primary malignant ulcers may be assumed to result from other causes of ulceration, and malignant transformation of a chronic ulcer may become apparent only after an ulcer fails to respond as expected to treatment. Diagnosis is dependent upon histologic confirmation of malignancy. Ulcers that are enlarging or failing to heal despite treatment, occurring in scars, or with exophytic or irregular wound edges probably warrant biopsy to rule out malignancy, but a standard of care has not been determined in large studies.

Drugs

Drugs associated with the development of leg ulcers include warfarin, heparin, and hydroxyurea.

- **Warfarin:** Warfarin skin necrosis is a microvascular occlusion syndrome that begins two to five days after beginning warfarin without concomitant heparin therapy and results from a transient hypercoagulable state [21, 22]. Pain is the initial symptom, followed by erythema, which then becomes hemorrhagic and necrotic. Retiform purpura may be adjacent to sites of skin necrosis. Warfarin-

induced skin necrosis is more common in women than men and is most likely to occur in fatty areas, such as breasts, hips, buttocks, and thighs. A biopsy of involved skin demonstrates bland thrombi in dermal blood vessels.

- **Heparin:** Heparin-induced thrombocytopenia is a thrombotic complication of heparin therapy resulting from the production of autoantibodies against platelet factor 4 in complex with heparin. Patients with heparin-induced thrombocytopenia may develop microvascular occlusion resulting in skin necrosis at sites of heparin injection or other sites, such as the distal extremities or nose. The initial manifestation is erythema that evolves to purpura, hemorrhage, and necrosis.
- **Hydroxyurea:** Hydroxyurea-related leg ulcers may occur in patients receiving chronic hydroxyurea therapy. The ulcers are clinically similar to ulcers of livedoid vasculopathy: painful, fibrous, persistent ulcers with surrounding atrophie blanche changes, typically near the malleoli or on the anterior lower leg [23]. The mechanism for ulcer development may involve drug-induced cytologic damage [23].

Brown recluse spider bite

Loxosceles reclusa envenomation is a rare cause of dermonecrotic lesions resulting in painful leg ulcers. The venom contains sphingomyelinase D, which may be responsible for neutrophil activation and skin necrosis (necrotic arachnidism).

Clinical features: The actual bite is often minimally painful; however, it is followed by the appearance of a tender erythematous plaque. The plaque develops central pallor followed by painful blistering and/or necrosis in about 40 percent of cases [24].

Diagnosis: The diagnosis is based upon witnessing the spider bite and correct identification of the spider. Most ulcers suspected to be caused by spider bites are actually due to infection or pyoderma

gangrenosum. In the absence of a witnessed bite and identification of the spider, other etiologies should be considered.

PATIENT EVALUATION

The evaluation of patients with leg ulcers begins with a clinical evaluation aimed at narrowing the differential diagnosis. Given that the vast majority of ulcers are caused by venous insufficiency, arterial insufficiency, or neuropathy, the initial goal should be to identify patients with these conditions. Alternative diagnoses should be considered when patients have features that are not consistent with these etiologies or fail to respond to appropriate treatments.

History

Key aspects of the patient history that should raise suspicion for venous, arterial, or neuropathic ulcers are reviewed in a table (table 2). Additional information that may aid in identifying other causes includes:

- History of trauma at ulcer site (traumatic ulcers, pyoderma gangrenosum [PG])
- Severe pain (ulcers due to arterial insufficiency, microvascular occlusion disorders, or PG)
- Rapid ulcer development (infectious ulcers, PG, brown recluse spider bite ulcer)
- Underlying thrombosis or coagulopathies (venous insufficiency ulcers, microvascular occlusion disorder ulcers, livedoid vasculopathy [LV])
- Underlying autoimmune disease or hematologic disease (ulcers due to vasculitis, PG, LV)
- Other chronic disease (ulcers due to arterial insufficiency [atherosclerosis], diabetic neuropathy [diabetes], PG [inflammatory bowel disease, arthritis], panniculitides [pancreatitis, alpha-1-antitrypsin deficiency, tuberculosis])
- Medication exposure (warfarin-, heparin-, or hydroxyurea-induced ulcers)
- Poor mobility (pressure ulcers)

● Smoking (ulcers due to thromboangiitis obliterans)

In addition, the clinician should review prior ulcer treatments. A failure to respond to treatment may suggest an incorrect diagnosis or malignant ulcer.

Physical examination

The physical examination serves to identify physical features of the ulcer (eg, location, size, shape) and associated cutaneous or non-cutaneous features that may aid in diagnosis. Findings that should raise suspicion for venous insufficiency, arterial insufficiency, and neuropathic ulcers should be reviewed. Because arterial insufficiency ulcers are common, routine palpation of pedal pulses is prudent.

Additional physical examination findings that may help to narrow the differential diagnosis include:

● Palpable purpura (ulcers due to small or small- and medium-vessel vasculitis)

● Retiform purpura or livedo racemosa (ulcers due to microvascular occlusion disorders or medium-vessel vasculitis)

● Nodules (ulcer due to medium-vessel vasculitis or panniculitis)

● Predilection for high-fat areas (ulcers due to calciphylaxis or **warfarin**)

● Atrophie blanche (livedoid vasculopathy or venous insufficiency ulcers)

● Livedo reticularis (ulcers due to microvascular occlusion disorders)

● Oily drainage (ulcers due to pancreatic panniculitis or alpha-1-antitrypsin panniculitis)

The physical examination should also include an assessment for clinical signs of secondary infection (eg, warmth, erythema, swelling, purulent drainage, malodor) or osteomyelitis (eg, visible bone, ability to probe to bone).

Biopsy

Biopsies are not necessary for the diagnosis of most ulcers, but can be helpful when the diagnosis is unclear or ulcers fail to respond to

therapy. Histopathologic examination may be particularly helpful when vasculitis, microvascular occlusion disorders, panniculitis, infection, or malignancy are in the differential diagnosis.

In general, biopsies for diagnosis are performed from the edge of an ulcer. A punch biopsy to subcutaneous fat or a wedge biopsy from the ulcer edge are recommended. A biopsy from purpura or early necrosis at the ulcer edge may be particularly informative. A biopsy site may subsequently ulcerate in cases of PG (pathergy) and patients should be informed of this risk. Biopsies to provide tissue for culture are also useful for evaluating ulcers for primary or secondary infection.

Additional tests

The need for serologic, radiologic, or microbiologic studies is determined by the disorders being considered. Such studies may be performed to confirm ulcer etiology or to evaluate for an associated underlying disease. Additional tests also may serve to evaluate for complications such as wound infection or osteomyelitis. However, routine wound swab cultures are not recommended in the absence of clinical signs of infection because bacterial colonization of ulcers is common [4].

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Chapter 3

Principles of lower extremity PAD management

The management of patients with lower extremity PAD is aimed at relieving symptoms and lowering the risk of cardiovascular disease progression and complications. Patients with PAD exhibit a wide range of symptoms and associated effects on daily function.

The treatment of symptomatic lower extremity PAD is based on a careful assessment of risk factors, medical comorbidities, compliance with pharmacologic treatments and follow-up care, and the subjective values and goals of the patient. Patients with ischemic pain or ulceration may necessarily require early intervention for limb salvage.

Medical management

Medical management involves cardiovascular risk factor reduction, lifestyle modification, and other pharmacologic therapies to reduce the risk of atherosclerotic disease progression [1,2] With aggressive medical management, regression of noncalcified atherosclerotic lesions may be possible [3]. Regular exercise and weight reduction are also important.

Risk factor modification

PAD is regarded as a coronary heart disease risk equivalent. Major cardiovascular practice guidelines for the management of patients identified with PAD (asymptomatic or symptomatic) recommend secondary prevention measures to reduce the risk of future cardiovascular events and impact management and amputation risk (figure 2) [4,5]. WIfI restaging can also be used to help to assess the adequacy of intervention [4].

GLASS

The Global Anatomic Staging System (GLASS) is an anatomic classification (table 3) that grades the level of disease in the femoropopliteal and infrapopliteal segments of the preferred target artery path [6]. These are combined to provide an overall grade of complexity for lower extremity interventions. potentially limit the progression of atherosclerosis [1,2,7-9].

Preventive therapies

Preventive therapies include antiplatelet therapy, smoking cessation, lipid-lowering therapy, and treatment of diabetes and hypertension. Some of these treatments can also reduce the risk of periprocedural complications and also may improve symptoms or the patency of interventions.

Antithrombotic therapy

Based upon randomized trials showing a significantly reduced risk for future adverse cardiovascular events, major cardiovascular consensus guidelines recommend long-term antiplatelet therapy (aspirin or clopidogrel) for patients identified with symptomatic lower extremity PAD [1,2,4]. For individuals identified with PAD who are asymptomatic, treatment with aspirin is reasonable. We do not recommend dual antiplatelet therapy in patients with PAD in the absence of other indications (eg, drug-eluting stent) given the increased risk of bleeding in the absence of proven benefit.

The effectiveness of antiplatelet therapy for the secondary prevention of adverse cardiovascular events (eg, myocardial infarction [MI], stroke, vascular death) was demonstrated in the Antithrombotic Trialists' Collaboration [10-12]. Specifically among patients with PAD, in a meta-analysis that included 18 trials involving 5269 patients with PAD (symptomatic and asymptomatic), aspirin therapy (alone or in combination with dipyridamole) was associated with a nonsignificant reduction for the primary endpoint (composite endpoint of nonfatal MI, nonfatal stroke, and cardiovascular death) but a significant reduction

in the secondary outcome of nonfatal stroke (relative risk [RR] 0.66; 95% CI 0.47-0.94) [13]. There were no significant differences in other individual secondary outcomes (nonfatal MI, major bleeding).

While aspirin remains the first-line agent of choice, clopidogrel is an alternative to aspirin [1]. Alternative antiplatelet agents (clopidogrel, ticagrelor, vorapaxar) have been studied in the PAD patient population [14-21]. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel (75 mg/day) had a modest, although significant, advantage over aspirin (325 mg/day) for reducing the risk for the combined outcome of ischemic stroke, MI, or vascular death in 19,185 patients with a recent stroke, MI, or symptomatic PAD (relative risk reduction 8.7 percent, 95% CI 0.3 to 16.5 percent) [22]. In a subgroup analysis, the benefit for clopidogrel over aspirin was mainly driven by patients with PAD, for whom there was a 23.8 percent relative risk reduction (95% CI 8.9 to 36.2 percent).

Some trials suggest that ticagrelor may provide additional benefit for preventing cardiovascular events [15-17]. Direct comparisons between ticagrelor and clopidogrel in patients with symptomatic PAD have found no significant differences [18, 20]. In the PEGASUS-TIMI 54 trial, 21,162 patients with prior MI one to three years prior were randomly assigned to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, all on a background of low-dose aspirin [17]. Among PAD patients with prior MI (1143 patients; 5 percent of the total), ticagrelor reduced the absolute rate of major adverse cardiovascular event by 4.1 percent and significantly reduced the risk for peripheral revascularization (hazard ratio [HR] 0.63, 95% CI 0.43-0.93). However, there was a 0.12 percent absolute excess of major bleeding.

In the EUCLID trial, 13,885 patients with predominantly symptomatic PAD were randomly assigned to single-agent therapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily) [19, 20]. The rate of ischemic stroke was significantly reduced for clopidogrel compared with ticagrelor (1.9 versus 2.4 percent; HR 0.78, 95% CI 0.62-0.98),

but there were no significant differences between the groups for the composite primary outcome (cardiovascular death, MI, or ischemic stroke; 10.8 versus 10.6 percent) or other outcomes (death, MI, acute limb ischemia, the need for revascularization, major bleeding). More patients receiving ticagrelor discontinued treatment due to dyspnea or minor bleeding.

Vorapaxar is a novel antagonist of protease-activated receptor (PAR-1), which is located on platelets, vascular endothelium, and smooth muscle and is the primary receptor for thrombin on human platelets [23]. In the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50), among patients with symptomatic lower extremity PAD, vorapaxar (administered with other antiplatelet agents) reduced the rate of first acute limb ischemia events, particularly among those who had undergone revascularization [24-27].

No benefit over aspirin has been established for vitamin K antagonists for reducing mortality in those with PAD. A systematic review that identified nine small trials involving 4889 patients noted no significant difference in mortality for anticoagulation versus control or versus aspirin following lower extremity bypass procedures, and the rate of major bleeding events was increased [28]. Similarly, in the later Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, a combination of warfarin (target international normalized ratio [INR] 2 to 3) plus antiplatelet therapy was not more effective compared with aspirin alone for preventing cardiovascular morbidity in patients with PAD [29].

Recent data suggest the benefit of combined antiplatelet and antithrombotic therapy in PAD [30-32]. A multicenter trial (COMPASS) randomly assigned over 27,000 patients with stable coronary or peripheral artery disease to a low dose of rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban (5 mg twice daily) plus placebo, or aspirin (100 mg once a day) plus placebo [30]. At a mean follow-up of 23 months, rivaroxaban plus aspirin significantly

reduced cardiovascular mortality and ischemic stroke compared with aspirin alone. In a prespecified subgroup analysis among 7470 subjects with PAD, rivaroxaban plus aspirin reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared with aspirin alone (5 versus 7 percent; HR 0.72, 95% CI 0.57-0.90), and major adverse limb events (1 versus 2 percent; HR 0.54, 95% CI 0.35-0.82) [32]. Rivaroxaban alone compared with aspirin alone did not significantly reduce the composite endpoint, but there was a trend toward reduced major adverse limb events. Rivaroxaban increased the risk of major bleeding (3 versus 2 percent) whether used alone or in combination. A direct comparison between low-dose rivaroxaban and clopidogrel would be useful before rivaroxaban could be considered an alternative to clopidogrel, which has previously shown in the CAPRIE trial to have provided an additional benefit over aspirin alone in reducing adverse limb events. An essential question is whether the observed improvements in limb outcomes outweigh the risk of bleeding, and if so, for which PAD patients.

Smoking cessation

Numerous epidemiological and observational studies show that smoking cessation reduces adverse cardiovascular events and the risk for limb loss in patients with PAD, but smoking cessation may be difficult to accomplish. Consensus guidelines recommend smoking cessation for all patients with PAD. The patient should be assessed for willingness to quit smoking and assisted in finding resources (eg, behavioral modification) to help with this goal. Follow-up for smoking cessation therapy should also be arranged. Nicotine replacement therapy and use of other pharmacologic adjuncts (varenicline or bupropion) should be considered. Nicotine replacement therapy does not appear to be associated with any increase in adverse cardiovascular events.

Lipid-lowering therapy

Lipid-lowering therapy with at least a moderate dose of a statin, irrespective of the baseline LDL cholesterol, is recommended for all patients with atherosclerotic cardiovascular disease. Examples of outcomes with the use of statin therapy among patients with PAD include the following [33-36]:

In the Heart Protection Study, among 6748 patients who had PAD, there was a 22 percent relative risk reduction in the first major vascular event for those randomized to simvastatin (40 mg) compared with placebo [33]. The absolute reduction in first major vascular event was 63 (standard error [SE] 11) per 1000 patients with PAD and 50 (SE 7) per 1000 without preexisting PAD.

In a five-year prospective study, patients undergoing major lower extremity amputations and who were on medium-intensity and high-intensity statin therapy had improved survival at one year compared with those who were not on similar statin therapy [37].

The effect of statin therapy in patients with chronic limb-threatening ischemia was evaluated in a retrospective study of 931 patients (1019 affected limbs) who underwent first-time revascularization (endovascular or surgical) over a nine-year period (2005 to 2014) [34]. Discharge on the recommended intensity of statin therapy was associated with lower mortality (HR 0.73; 95% CI 0.60-0.99) and lower major adverse limb event rate (HR 0.71; 95% CI 0.51-0.97) over a median follow-up of 380 days.

The effect of PCSK9 inhibition with evolocumab was evaluated in 3642 patients with PAD from the FOURIER trial [38]. The primary composite endpoint (cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, coronary revascularization) was significantly reduced for those with PAD randomized to evolocumab compared with placebo (HR 0.79; 95% CI 0.66-0.94). Evolocumab also reduced the risk of major adverse limb events in all patients (HR 0.58; 95% CI 0.38-0.88) with consistent effects among those with and without known PAD.

Glycemic control

Although it is unknown whether aggressive serum glucose control decreases the likelihood of adverse cardiovascular events in patients with lower extremity PAD, treatment of diabetes can be effective for reducing complications. However, the CANagliflozin cardioVascular Assessment Study (CANVAS) Program identified new safety concerns [39]. The amputations in the CANVAS program occurred more often in those with a prior history of PAD or prior amputation and were primarily below the ankle (ie, toe, transmetatarsal amputation). Recommendation for control of blood glucose levels is an A1C goal of <7.0 percent. Less stringent goals may be appropriate for some patients (eg, older patients and those with comorbid conditions) to avoid morbidity associated with hypoglycemia.

Antihypertensive therapy

Hypertension is a major risk factor for PAD. However, there are no data evaluating whether antihypertensive therapy alters the progression of PAD. Nevertheless, hypertension should be controlled to reduce morbidity from cardiovascular and cerebrovascular disease [40]. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril (10 mg per day) significantly reduced the rates of death, MI, and stroke in a broad range of patients, including those with asymptomatic or symptomatic PAD [41]. In a follow-up study looking at the PAD patients, the relative benefit of ramipril was similar in patients subdivided by levels of ABI [42]. Given that event rates were higher in those with an ABI <0.9, the absolute benefits are approximately twice as large in this group (50 per 1000 events prevented) compared with those with an ABI >0.9 (24 per 1000 events prevented).

Diet and exercise

Healthy diets are associated with lower cardiovascular disease events. Relevant guidelines on lifestyle management have been issued from the American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC).

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Chapter 4

Specific management of PAD syndromes

Asymptomatic PAD

Although those with asymptomatic PAD (defined as an abnormal ABI) may not report exertional pain, lower extremity function may nonetheless be impaired as evidenced by slow walking speed or poor balance. Whether those with asymptomatic PAD should undergo repeat ABI testing and with what frequency has not been established, but repeat testing may be useful in higher-risk patients. It is also important to note that some asymptomatic PAD patients, particularly those with diabetes, can develop limb-threatening ischemia without an antecedent history of claudication.

It is unknown if specific therapies, in addition to risk factor modification, can improve functional abilities or quality of life. As an example, it is unclear if antiplatelet therapy is beneficial for these patients. In trials of patients with asymptomatic PAD, aspirin compared with placebo did not significantly reduce the incidence of cardiovascular events [1-3]. Nevertheless, given the systemic nature of atherosclerotic disease, it is reasonable to treat patients with PAD who do not exhibit symptoms.

PAD with Claudication

The initial treatment for exertional pain (ie, claudication) is a supervised exercise program (algorithm 2) [4]. Patients must be screened for sufficient cardiopulmonary reserve and other medical comorbidities for their ability to tolerate an exercise program. The addition of the phosphodiesterase inhibitor, cilostazol, may also improve symptoms. Statin therapy may also improve pain-free walking time in patients with claudication, but the evidence for this is conflicting. There is no

evidence that beta blocker therapy for treatment of high blood pressure worsens claudication.

Without treatment, the natural history of claudication is a slow progressive decline in the distance the individual is able to walk before the onset of pain. However, with intensive medical management (risk factor reduction, exercise therapy, pharmacologic therapy), among patients with claudication and no diabetes or renal dysfunction, less than 5 percent will develop any signs of limb-threatening ischemia, and the risk of major amputation is exceedingly low (<1 percent per year). The risk for other adverse cardiovascular events (eg, stroke, heart attack) is greater than the risk for adverse limb outcomes [5-7].

Symptoms should be reevaluated after conservative treatments (risk factor reduction, exercise therapy, pharmacologic therapy) have been instituted and allowed to have an effect. If claudication symptoms persist and the patient has been responsive to adjusting his/her lifestyle, the patient may be a candidate for an endovascular or open intervention depending on the location and severity of lesions and medical risk. Some patients with severe symptoms, particularly those with more proximal disease (aortoiliac) may benefit more from earlier, rather than later, intervention [8]. Patients with symptomatic PAD are at risk for developing new or recurrent lesions in the same or other vascular beds, which underscores the need for ongoing follow-up.

PAD with Ischemic rest pain or tissue loss

Once a patient develops ischemic rest pain or tissue loss, the natural history often involves a persistent increased risk of major limb amputation unless there is some form of intervention to improve arterial perfusion. In the interim prior to intervention, and for those who are not candidates for intervention, it is appropriate to aggressively manage the patient's pain. Some patients are poor candidates for any type of revascularization procedure (endovascular, surgical) because of concomitant diseases or unfavorable anatomy. Medical therapies would be desirable in such patients. Therapies that have been investigated include prostaglandins, therapeutic angiogenesis, stem

cell therapy, and spinal cord stimulation; however, none of these are recommended. The presence of ischemic ulcers/gangrene influences the timing of debridement, revascularization, and definitive coverage/closure.

In general, for patients with wet gangrene or abscess, the wound should be debrided or drained immediately regardless of the anticipated need for revascularization. The dressing choice depends upon the level of anticipated drainage and the size of the wound. Dead space is usually managed with gauze packing. The extremity should be revascularized as soon as safely possible, if needed, after drainage/debridement and control of the infection.

For patients with dry gangrene without cellulitis, the limb should be revascularized first. The wound dressing is protective, reducing the risk for trauma or infection. The wound should be lightly wrapped with a bulky dry gauze bandage, avoiding excess pressure that could aggravate ischemia. Following revascularization, the wound should be monitored closely for signs of healing, or for tissue necrosis/drainage that may indicate a need for further debridement.

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PART II

Revascularization Treatment in PAD – Radiation Exposure Relevant Research

Chapter 1

Revascularization treatment in PAD

The Global Vascular Guidelines for the management of chronic limb-threatening ischemia provide a framework for evidence-based lower extremity revascularization, including recommendations for endovascular intervention or lower extremity surgical bypass [1].

Indications

For those with significant or disabling symptoms unresponsive to lifestyle adjustment and pharmacologic therapy, intervention (percutaneous, surgical) may be reasonable. In the absence of limb-threatening ischemia, symptoms of PAD tend to remain stable with medical therapy. Performing prophylactic intervention, whether percutaneous or surgical, in patients with minimal claudication provides little benefit, may cause harm, and is not indicated.

For patients with limb-threatening ischemia (eg, rest pain, ulceration), revascularization is a priority to establish arterial blood flow [2]. Some patients with acute thrombosis superimposed on chronic stenosis or occlusion (ie, acute-on-chronic ischemia) may benefit from thrombolytic therapy.

Once the decision has been made to intervene, a three-step integrated approach (PLAN) is suggested that includes Patient risk estimation, Limb staging using WIfI [3], and determining the ANatomic pattern of disease using the Global Anatomic Staging System (GLASS) [1].

For patients over 65 years of age, comprehensive geriatric assessment may improve outcomes following elective lower extremity bypass. In a trial that included 176 patients undergoing lower extremity bypass surgery or abdominal aortic aneurysm (AAA) repair, length of stay was reduced for those randomly assigned to comprehensive geriatric assessment and optimization versus standard preoperative assessment (3.32 versus 5.53 days) [4]. Although the outcomes were

not stratified by the type of surgery, the major benefit shown is more likely to have occurred in the bypass group. The comprehensive assessment increased the number of new diagnoses (eg, pulmonary disease, chronic kidney disease, cognitive impairment) and influenced the number of patients who did not undergo surgery. There was a lower incidence of complications, including cardiac complications (8 versus 27 percent), bladder/bowel complications (33 versus 55 percent), and delirium (11 versus 24 percent). Patients in the comprehensive assessment group were also less likely to require discharge to a higher level of dependency. This trial underscores the need to accurately assess medical risk prior to undertaking elective vascular surgery in older adults.

Choice of intervention

Among those with appropriate indications for intervention, determining whether percutaneous or surgical revascularization is the more appropriate initial treatment depends upon a myriad of factors, including location and extent of disease, patient's comorbidities and risk for the intervention, and patient preference.

Endovascular interventions have a lower periprocedural risk in the short term, but durability has not been comparable to surgical revascularization. For patients with claudication, the Society for Vascular Surgery suggests that a minimal effectiveness threshold for invasive therapy should be a >50 percent likelihood of sustained clinical improvement for at least two years [5]. Freedom from hemodynamically significant restenosis in the treated limb is considered a prerequisite for this goal. The majority of patients presenting with limb-threatening ischemia can be offered a reasonable attempt at limb salvage. Freedom from pain or sustained healing of areas of tissue loss may be acceptable goals even in the absence of sustained patency of the treated lesion, particularly among patients who are poor candidates for surgical revascularization. Overall, only approximately 25 percent of patients with critical limb ischemia require

amputation within one year. However, for some patients, primary amputation may be the best course of therapy.

Given the widespread availability of percutaneous procedures, major vascular society guidelines recommend initial percutaneous revascularization. Surgery is reserved for those with arterial anatomy for which a percutaneous approach is not likely to provide a durable clinical success, provided the patient has an acceptable risk for surgery [1, 6-9]. Lesions that display unfavorable anatomy for a percutaneous approach have one or more of the following features, which reflect more extensive disease and are typically associated with more severe symptoms:

- Long-segment stenoses
- Multifocal stenoses
- Eccentric, calcified stenoses
- Long segment occlusions

The issues regarding the choice of intervention differ depending upon clinical manifestations, goals of care, and the affected vascular bed.

Perioperative medication management

Whether to continue or discontinue antiplatelet agents prior to vascular surgical intervention is controversial [10, 11]. Few studies have focused specifically on vascular surgery patients who should be taking aspirin (or clopidogrel) as a recommended strategy for long-term cardiovascular risk reduction. Most intrventionists generally maintain patients on prescribed antiplatelet therapies.

In the PeriOperative ISchemic Evaluation 2 (POISE-2) trial, perioperative aspirin use increased the risk of bleeding but had no effect on perioperative (30 day) mortality. Whether these results apply to vascular surgery patients was addressed in a subgroup analysis of POISE-2 that included 603 patients [12]. Among these were 272 patients undergoing surgery for peripheral occlusive disease. Excluded from the POISE-2 trial were patients with carotid occlusive disease and patients with bare metal coronary stents placed fewer than six weeks before the surgery or drug-eluting coronary stents less

than one year before surgery. As with the overall results, there was no significant difference for the primary outcome (composite of death or myocardial infarction at 30 days) for those allocated to aspirin compared with placebo (15.8 versus 13.6 percent; hazard ratio [HR] 1.16, 95% CI 0.62-2.17). Perioperative withdrawal of chronic aspirin therapy did not appear to increase vascular occlusive complications. However, while there was an increased risk of major or life-threatening bleeding, the difference was not statistically significant among vascular surgery patients taking aspirin. The results of this study (positive and negative) need to be viewed with caution as the number of events was small and the subgroup analysis was underpowered.

Adjuncts to improve patency

Antithrombotic therapy

Definitive data to support the use of antiplatelet and antithrombotic therapy to improve the patency of lower extremity revascularization are overall lacking. Antiplatelet therapy may benefit those undergoing prosthetic bypass, and although anticoagulation with vitamin K antagonists is not routinely used following surgical revascularization, it may be useful in the following situations: following vein bypass for those with either a suboptimal conduit or compromised distal runoff, or following prosthetic graft bypass to reduce the ischemic consequences of graft thrombosis.

Whether the addition of another antiplatelet agent to aspirin (ie, dual antiplatelet therapy) offers any additional benefit for those who have undergone lower extremity percutaneous revascularization remains debated.

A new protease-activated receptor (PAR-1) antagonist, vorapaxar, may offer benefit, but further studies are needed to identify its role following revascularization. In the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50) trial discussed above, 3787 patients with symptomatic lower extremity PAD were included [13,14]. In a follow-up analysis [15], vorapaxar

significantly reduced the risk of first acute limb ischemia (ALI) event compared with placebo (HR 0.58; 95% CI 0.39-0.86) and also significantly reduced total ALI events (94 versus 56 events). The majority of first and recurrent ALI events occurred in those with symptomatic PAD. The causes of the 150 critical limb ischemia events in the PAD group were surgical graft thrombosis in 93 (62 percent), native vessel in-situ thromboses in 37 (25 percent), stent thromboses in 14 (9 percent), and thromboembolism in 6 (4 percent).

Concern over paclitaxel

A number of medical therapies aimed at preventing restenosis related to percutaneous angioplasty have been tried, but only local delivery of the drug paclitaxel has been shown to improve the longevity of interventions for lower extremity atherosclerotic disease. The outcomes of reported trials studying paclitaxel-coated devices have overwhelmingly used lesion-oriented outcome measures, such as target lesion revascularization (TLR) or primary restenosis, rather than functional or patient-oriented measures, such as increased limb salvage or improved walking distance.

However, the overall safety of paclitaxel-coated balloons and stents placed into the legs of patients with PAD has come into question. Based on a review of long-term follow-up data from premarket randomized trials, the US Food and Drug Administration (FDA) has urged that health care providers should consider the potential benefits of paclitaxel-coated devices (ie, reduced reinterventions) in individual patients along with potential risks (ie, late mortality) before using paclitaxel-coated devices for the treatment of PAD [16]. The long-term data from the pivotal premarket trials were presented by the FDA at a public meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee [17]. In the FDA's meta-analysis of these trials (1090 patients), overall mortality at five years was significantly increased for patients treated with paclitaxel-coated devices compared with those treated with uncoated devices (19.8 versus 12.7 percent, relative risk 1.57, 95% CI 1.16-2.13). These results confirmed a meta-

analysis by Vascular InterVentional Advances (VIVA) physicians of patient-level data provided by manufacturers (hazard ratio of 1.38, 95% CI 1.06-1.80) [18] and an earlier meta-analysis (mortality risk ratio 1.93; 95% CI 1.27-2.93) [19]. Nevertheless, the Panel, the FDA, and others agree that the magnitude of the potential increased mortality should be interpreted with caution given the multiple limitations in the available data (eg, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths) [20-22].

Outcome measures

Outcomes of revascularization may be measured anatomically, hemodynamically, and functionally. While anatomic patency and hemodynamic success are important, the primary reason to perform an intervention is symptom relief and longterm clinical success. Following intervention, clinical success is often higher than anatomic success. Clinical failures are only partially related to anatomic patency of the treated area, and other factors, such as progression of disease in the inflow vessels, in the treated vessel, and in the outflow tract, are also implicated.

The Society for Vascular Surgery (SVS) has adopted objective performance goals to assess cross-platform interventions in a patient-centric manner [23, 24].

- Major adverse cardiovascular events (MACE)
- 30-day major adverse limb events (MALE)
- 30-day amputation rate
- Amputation-free survival
- Freedom from MALE

Anatomically, the patency of the intervention, as defined by the SVS reporting standards, allows one to assess the time to primary failure

(ie, occlusion or need for intervention) and the time to final failure after multiple interventions and revisions.

Primary patency: Refers to patency that is obtained without the need for an additional or secondary surgical or endovascular procedure.

Assisted primary patency: Refers to patency achieved with the use of an additional or secondary endovascular procedure as long as occlusion of the primary treated site has not occurred.

Secondary patency: Refers to patency obtained with the use of an additional or secondary surgical procedure once occlusion occurs.

Hemodynamic success is defined as an increase in ankle brachial index (ABI) of at least 0.15. Immediate and long-term hemodynamic success (ABI >0.15) after percutaneous procedures is directly related to tibial runoff [25]. Most studies have shown an appropriate increase in ABI after intervention. The magnitude of change may or may not correlate with symptomatic improvement.

Postprocedure surveillance

Periodic clinical evaluation and post-procedure surveillance helps identify problems that can contribute to thrombosis and potentially limb loss. The SVS WIfI Classification is recommended to stage the limb in patients with chronic limb-threatening ischemia and to assess the response to therapy [3]. Following vascular interventions, angioplasty sites, stents, and vascular bypass grafts are also carefully monitored using duplex ultrasonography. The surveillance schedule depends on the nature of the intervention. At a minimum, patients should be evaluated twice a year for any new symptoms. The main complications are graft or stent thrombosis, vein graft stenosis, in-stent stenosis, and new native vessel stenotic lesions. There are three major time periods for failure after intervention.

- Failure in the immediate or early postoperative period (<30 days) is most often due to technical complications or judgment errors. Other causes include inadequate outflow, infection, and an unrecognized hypercoagulable state.

- Failure between 30 days and two years is most often the result of myointimal hyperplasia within the endovascular treated areas, within the vein graft or at anastomotic sites.
- Late endovascular and late graft failure is usually due to the natural progression of atherosclerotic disease.

PROGNOSIS

The overall prognosis of the patient with PAD depends on the specific risk factors for PAD, the specific vascular beds that are more predominantly affected, and the presence of coronary heart disease and other comorbidities [26-28]. Estimates for limb and cardiovascular outcomes at five years in patients with claudication are as follows:

Prognosis for limb morbidity in patients with IC

Stable claudication in 70 to 80 percent, worsening claudication in 10 to 20 percent, and limb-threatening ischemia (ie, critical limb ischemia) in 1 to 2 percent [29,30].

Prognosis for cardiovascular morbidity and mortality in patients with IC

Nonfatal myocardial infarction or stroke in 20 percent, and death in 15 to 30 percent (three quarters due to cardiovascular causes); an association between cardiovascular disease and PAD has been noted in multiple studies [26, 31]. The importance of PAD as a marker for coexistent coronary artery disease cannot be understated.

Prognosis for limb morbidity and mortality in patients with CLI

Among the 1 to 2 percent of patients who develop critical limb ischemia, outcomes have improved over time, related to improved medical management [32, 33], and possibly the more liberal use of endovascular intervention [34]. Even among those without a revascularization option, amputation-free survival has improved [35]. Overall (all comers), at one year, 45 percent of patients will be alive with both limbs, 30 percent will have undergone amputation, and 25

percent will have died. At five years, more than 60 percent of patients with critical limb ischemia will have died. For patients with nonreconstructible disease at one year, approximately 55 percent will be alive without amputation (range 40 to 69 percent); 20 percent of patients will have died (range: 12 to 32 percent), and 34 percent will have undergone major amputation (range: 25 to 45 percent) [35].

These general estimates do not apply equally to all patients. Atherosclerotic vascular disease tends to be more aggressive in patients with diabetes and lower extremity PAD with amputation rates that are five to 10 times higher compared with nondiabetic patients with PAD. Sensory neuropathy and increased susceptibility to infection contribute to the increased amputation rate. The prognosis for both limb loss and survival is significantly worse in patients with diabetes and end-stage renal disease, and those who continue to smoke [36].

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Chapter 2

Relevant Research 3:

Occupational exposure during endovascular aneurysm repair (EVAR) and aortoiliac percutaneous transluminal angioplasty (PTA) procedures

Introduction

Atherosclerosis of aortoiliac arteries, abdominal aorta and below the knee arteries can cause intermittent claudication, gangrene, limb ischemia and loss of a limb [1–3]. Symptoms of peripheral artery disease include rest pain, leg numbness, weak pulse in the lower extremities, coldness on lower leg or feet. PTA is the most common fluoroscopically guided inter- vention for the treatment of peripheral artery disease [4].

The most frequent form of aortic aneurysm is the abdominal aortic aneurysm (AAA) [5]. Low blood pressure, abdomen pain and death are some of the consequences of a rap- tured aneurysm [6]. Repair of AAAs is recommended when the diameter of the aneurysm is greater than 5.5 cm and 5 cm for males and females, respectively [6]. Patients with an abdominal aortic aneurysm can be treated with either open surgery or endovascular surgery. EVAR is a fluoroscopically guided procedure with lower morbidity and mortality rates than the open surgery [7, 8].

Care of vascular diseases with fluoroscopically guided interventions reduces the duration of stay in hospital as well as morbidity and

mortality of patients [7-9]. However, the use of fluoroscopy in PTA and EVAR procedures leads to considerable radiation doses for interventionalists. Only a few studies have evaluated the radiation exposure of primary operator's radiosensitive organs such as thyroid or eye lenses during these procedures. The aim of our study was to determine the radiation exposure of primary interventionalist's different body parts during EVAR and PTA procedures. The efficacy of a radioprotective drape was also evaluated.

Materials and methods

Dosimetric data for 36 consecutive aortoiliac PTA proce- dures and 17 consecutive EVAR procedures were collected prospectively. The procedures were performed by three experienced interventionalists.

The following data were recorded for all patients: total fluoroscopy time, DAP, PSD and the number of digital subtraction angiography (DSA) series. For each DSA, the angulation of the C-arm, tube potential, DAP, PSD and filtration were also recorded. Positioning of the C-arm in left/ right (LAO/RAO) direction was between 0° and 45° for both procedures.

Occupational doses in both procedures were determined using thermoluminescence dosimetry (TLD) chips (TLD- 200, Hashaw, Solon, OH). TLDs were calibrated with the use of a radiographic system and an ionization chamber (Radcal Corporation, California, USA). One hundred and twenty TLDs were used. Operators were equipped with 0.5 mm Pb equivalent aprons, protective eyewear and thyroid collars. At the beginning of each procedure, TLD chips were placed on the left side of the head, on the protective eye-wear, over and underneath the thyroid collar, on chest level over and underneath the apron and on the middle finger of both hands of the primary operator. The operating room was equipped with both a ceiling-suspended transparent shield and a lead curtain underneath the patient table.

Effective dose (ED) was calculated using the Niklason algorithm [10].

$E = 0.02 (H_{OC} - H_{UA}) + H_{UA}$ (1)

where HOC is the dose over the thyroid collar and HUA is the dose under the apron. Estimation of the effective dose with this algorithm is independent of apron's thickness.

To evaluate the efficacy of a radioprotective drape, experiments were performed using two physical anthro- pomorphic phantoms (Rando-Alderson Research Labs, CA, USA) and a 0.25 mm Pb equivalent drape (Ecolab, Saint Paul, Minnesota, USA). The phantom operator was placed in the position of the primary operator. The second phantom was oriented in the head-first supine position on the operating table. In each experiment, 16 thermoluminescence dosimeters were placed on the phantom operator in the following body regions: forehead, right and left side of the head, right and left eye, neck, abdominal and thoracic region, genitals (Fig. 1).

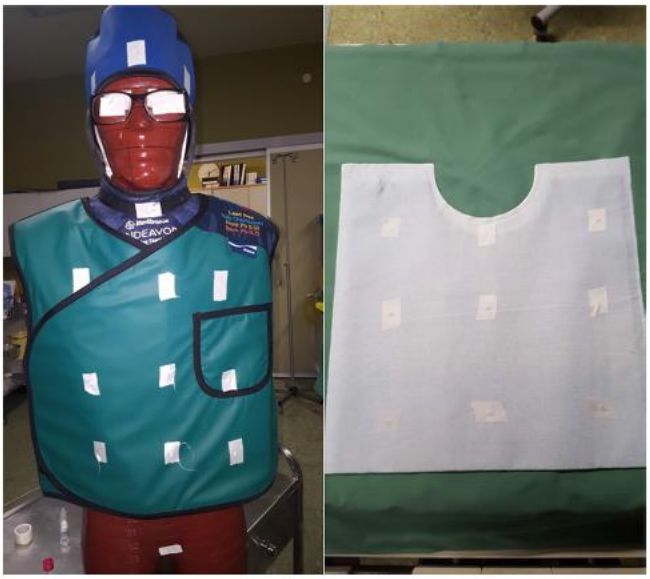

Fig. 1 TLDs placed on Rando anthropomorphic phantom and on drape

Three experiments were performed to evaluate the effect of drape positioning on automatic exposure control (AEC) system. In the first case, the drape was not placed into the field. In the second case, the drape was placed slightly into the field and in the third case, about half

of the drape was placed into the field (Fig. 2). Total fluoroscopy time and the number of DSA runs were the same for all simulations.

Statistical analysis

Statistical analysis was performed using Prism Software (Graphpad, CA, USA), and Office Excel (Microsoft, WA, USA). D'Agostino's K-squared tests were used to deter- mine the distribution of the acquired values. Spearman rank correlation tests were used to evaluate the degree of association between radiation exposures measured at different body parts of the primary operator and fluoroscopy time. Mann–Whitney U tests were used for the comparison of the values between EVAR and PTA procedures. A P value lower than 0.05 indicates a significant difference between the compared values.

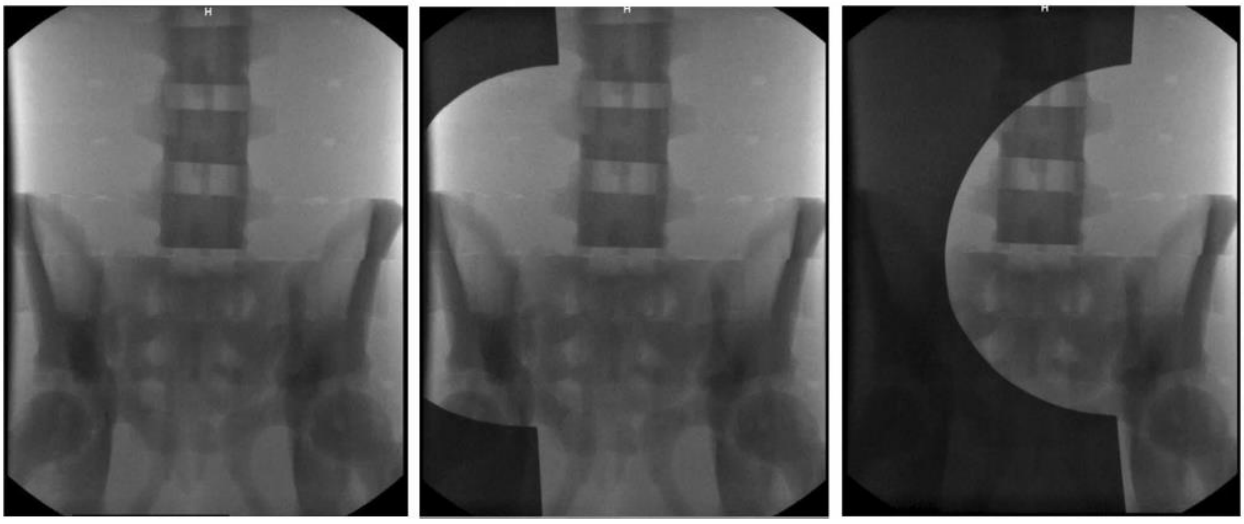

Fig. 2 Positioning of the drape in the first experiment (left), second experiment (middle), third experiment (right)

Results

There was a statistically significant difference in fluoroscopy time (P = 0.0008) and DAP (P < 0.0001), between PTA and EVAR procedures (Table 1).

Table 1 Median Values of Radiation Exposure Parameters for PTA and EVAR procedures

Parameter	Procedure	Value			
		Median	SD	Range	*P* value
Fluoroscopy time (min)	EVAR	24.5	14.3	13.6–64.7	0.0008
	PTA	14.1	17.9	4.7–88.9	
Total DAP (Gy cm^2)	EVAR	124.3	156.9	41.4–627.1	< 0.0001
	PTA	23.1	61.2	37.0–296.0	

Table 2 presents occupational doses of the primary operator, for EVAR and PTA procedures, respectively. The highest radiation doses were measured for the hands of the operator in both procedures. Correlation between radiation exposures measured at different body parts of the interventionalist and fluoroscopy time were ranged from 0.39 to 0.57 (P value ranged from < 0.001 to 0.03) for PTA procedures and from 0.70 to 0.82 (P < 0.001) for EVAR procedures. Figures 3 and 4 show the correlations between chest dose over the apron, right-hand dose, thyroid dose over the collar, eye lens dose and fluoroscopy time for the primary operator in PTA and EVAR procedures.

Table 2 Occupation doses of primary operator for EVAR and PTA procedures

Procedure	Median (μGy)	SD	ED (μSv)	Range
EVAR			4.7 ± 1.4	1.5–19.6
Body part				
Head	35.7	37.4		5.8–132.1
Eyes	34.4	37.6		8.3–125.3
Chest (over the apron)	72.6	62.3		10.5–244.4
Chest (underneath the apron)	4.2	3.8		1.5–17.8
Thyroid (over the collar)	25.7	27.5		2.6–107.0
Thyroid (underneath the collar)	5.9	6.5		1.6–30.2
Left hand	76.9	111.9		13.3–418.7
Right hand	46.7	122.7		8.7–520.5
PTA			4.4 ± 3.6	1.0–11.0
Body part				
Head	10.6	27.1		3.4–141.8
Eyes	12.3	41.3		3.1–211.2
Chest (over the apron)	14.8	69.5		4.4–297.9
Chest (underneath the apron)	4.3	1.6		0.9–7.5
Thyroid (over the collar)	10.9	38.8		3.9–178.6
Thyroid (underneath the collar)	4.8	2.5		1.0–10.7
Left hand	39.6	355.0		4.9–1877.5
Right hand	22.4	143.2		2.7–636.2

Table 3 presents the maximum number of EVAR or PTA procedures an interventionalist can perform annually. The calculated maximum

workloads were based on the annual effective dose limit and equivalent dose to the lens of the eye limit recommended by ICRP as well as on median ED and eye lens doses presented in Table 2.

Table 3 Maximum permissible annual workload based on ED and eye lens doses

Procedure	Number of procedures (based on ED)	Number of procedures (based on eye lens dose)
EVAR	4255	581
PTA	4545	1626

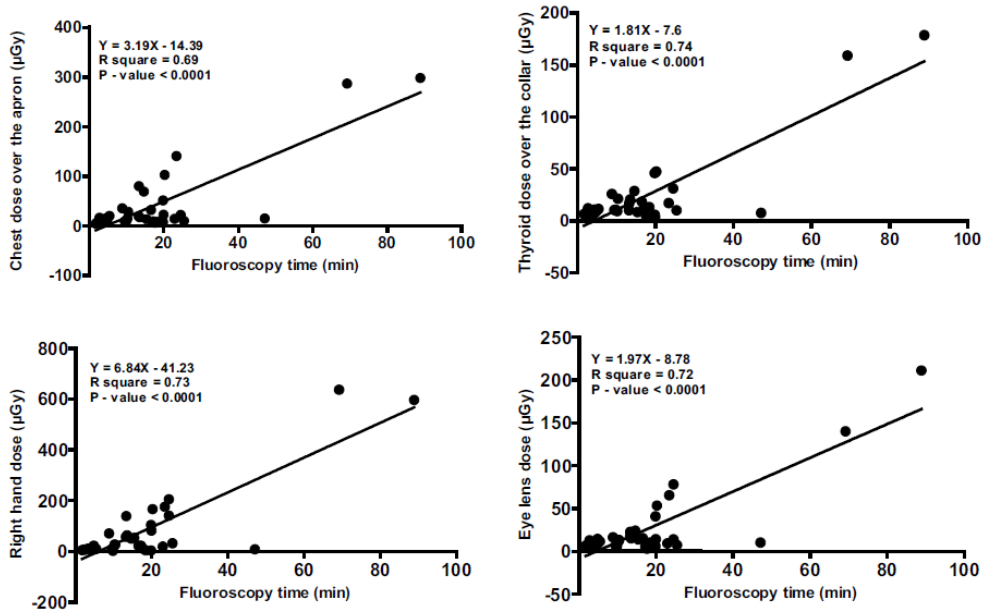

Fig. 3 Correlations between different body parts doses and fluoroscopy time in PTA procedures

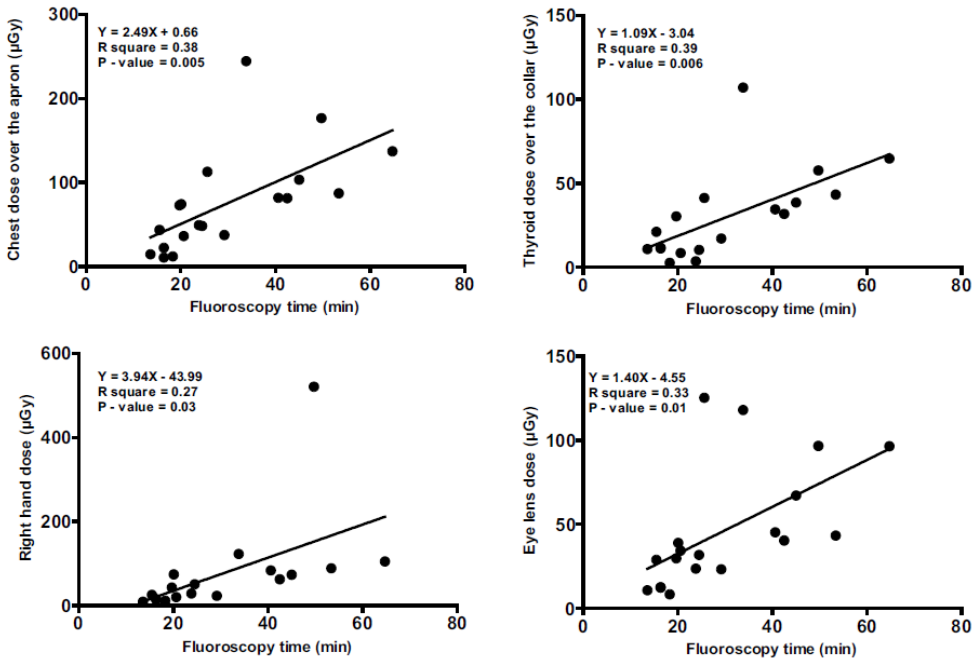

Fig. 4 Correlations between different body parts doses and fluoroscopy time in EVAR procedures

The results of this study show that the drapes significantly contribute to the operator's radioprotection. Specifically, radiation exposure of the abdominal area, genitals and thyroid, was reduced by an average of 59%, 60%, 65%, respectively, due to the use of the drape. Table 4 presents the reduction at different angulations of the C-arm and at the different body parts. However, drapes should be used with caution, as their misplacement increases exposure parameters, patient dose and occupational dose when AEC is activated. DAP and PSD were subtly different when the drape was placed slightly into the field. On the contrary, differences up to 20% were noted when half of the drape was placed into the field (Table 5).

Table 4 Reduction of the radiation exposure with the use of a radioprotective drape

Angulation of the arm			Percentage differences between radiation doses measured at different body parts with and without the radioprotective drape														
LAO	CRA	CAU	Right side of the head	Forehead	Left side of the head	Right Eye Lens	Left Eye Lens	Thyroid	Right HR	Right LR	Right IR	EPR	UMR	HGR	Left HR	Left LR	Left IR	Genitals
0°	0°	0°	17	38	47	43	47	53	18	41	36	26	45	31	43	37	36	52
15°	0°	0°	43	51	50	38	39	56	53	48	45	59	57	47	57	59	55	67
0°	15°	0°	27	77	74	78	76	75	74	80	73	69	77	76	76	74	74	56
0°	0°	15°	27	75	67	76	75	75	74	76	75	68	77	70	70	73	71	66

HR hypochondriac region, *LR* lumbar region, *IR* iliac region, *EPR* epigastric region, *UMR* umbilical region, *HGR* hypogastric region, *LAO* left anterior oblique, *CRA* cranial angulation angle, *CAU* caudal angulation angle

Table 5 Differences in DAP and PSD due to the placement of the drape into the field

Position of the drape	DAP (μGym^2)	PSD (mGy)
Out of the field	2218.3	88.9
Slightly into the field	2221.4	89.6
Half of the drape into the field	2769.6	111

Discussion

DAP and fluoroscopy time are directly related with the radiation exposure of the interventionalists. Tables 6 and 7 pre- sent fluoroscopy time and DAP reported in the literature for EVAR and PTA procedures, respectively. The large variation of the reported values can be attributed to the patient positioning and body characteristics, fluoroscopic equipment as well as operator's skills, training and experience [11, 12]. Tabulated data (Table 2) show that radiation exposure of the primary operator was higher in EVAR procedures than in PTA procedures. The highest radiation doses were measured for the operator's hands in both procedures. To the best of our knowledge, only two studies, Neto et al. [13] and Ho et al. [14], reported hand doses for the primary operator during EVAR procedures. Specifically, Ho et al. [14] reported a median hand dose of the chief surgeon equal to 34.3 μSv, while the respective dose reported by Neto et al. [13] was 2105.3 μSv. The right- and left-hand doses of the primary operator, presented in the current study, were 46.7 μSv and 76.9 μSv, respectively. Based on the literature, hand doses of the interventionalists during PTA procedures range from 21 to 190 μSv [13–15, 23, 24].

Eye lens doses during PTA procedures have been evaluated by a number of studies [13–15, 23–25]. The reported doses vary from 2.0 to 53.7 μSv. The wide range of these values indicates that several parameters including complexity of the procedures as well as the experience of the operator affect the radiation exposure of the interventionalists. The number of studies reporting eye lens doses during EVAR procedures is relatively small. The lower eye lens dose per EVAR procedure (9.7 μSv)

has been reported by Ho et al. [14]. This is 3.5 times lower than the respective dose presented herein. Of note, however, is that Ho et al. [14] placed the dosimeters within lead eyeglasses while we placed them externally. Concerning thyroid, high doses, i.e., 338.4 μSv and 58.8 μSv for EVAR and PTA procedures, respectively, were measured above the collar by Neto et al. [13]. These are 13.2 and 5.4 times higher than the corresponding values presented herein. These differences may be attributed to the absence of a ceiling-suspended transparent shield.

The proper use of a radioprotective drape leads to a significant reduction in occupational doses. The current study shows that the use of a drape reduces the eye lens dose to primary operator by an average of 59%. Significant reduction in the radiation exposure was also recorded for the abdominal region, thyroid and genitals. Further, a mean reduction up to 29%, 60%, and 60%, of the radiation exposure, was recorded for the right side of the head, the forehead and the left side of the head, respectively. These results are in agreement with the corresponding results presented in the literature [15–17]. The efficacy of the drape has been evaluated by a number of studies. To the best of our knowledge, this is the first study examining the effect of the positioning of drapes on AEC. Our results show that activation of AEC yields higher radiation dose for patients and personnel when the drape is included in the field. Specifically, DAP and PSD were increased by 20% when part of the drape was placed into the X-ray field. Radiation dose increases when a drape is in the X-ray field because AEC increases the exposure in an attempt to maintain image quality.

Our study has some limitations that should be considered. First, it was a single-center study. All measurements were taken in a specific interventional radiology suite. Second, the effect of procedural complexity on occupational doses, fluoroscopy time and DAP was not examined. Third, the evaluation of the radioprotective drape was carried out using physical anthropomorphic phantoms. A patient study is needed to confirm the effect of the drapes positioning on AEC.

Conclusion

During EVAR and PTA procedures, primary operator's organs are exposed to considerable radiation doses. The highest radiation doses were measured for the operator's hands in both procedures. Occupational radiation exposure can be reduced significantly using a radioprotective drape. However, the use of the drape needs caution as its misplacement could lead to higher doses for the patients and the operators.

Table 6 Reported total fluoroscopy time (FT) and DAP during EVAR procedures

Study	FT (min)	DAP (Gy cm^2)	Comments
Patel et al. [18]	19.5	97.3	
Sailer et al. [19]	19.6	116	
Hertault et al. [20]	27.3	41.2	
Ho et al. [14]	13.0	–	
Neto et al. [13]	29.3	–	
Blaszak et al. [21]	19.6	354.0	
Tuthill et al. [22]	13.1	31.6	Site A
	11.7	184.2	Site B
	9.0	80.2	Site C
	14.6	60.8	Site D
	11.2	162.5	Site E
This study	24.5	124.3	

Table 7 Reported total fluoroscopy time (FT) and DAP during PTA procedures

Study	FT (min)	DAP (Gy cm^2)
Heye et al. [23]	6.2	4.1
Ingwersen et al. [24]	7.2	–
Jensen et al. [25]	13.0	24.0
Ho et al. [14]	6.3	–
Neto et al. [13]	15.6	–
Power e al. [15]	8.2	24.6
Sigterman et al. [26]	13.0	108.0
McBridge et al. [27]	15.6	–
This study	14.1	23.1

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PART III

Feasibility of ischemic leg ulcer healing using percutaneous techniques: a real-life study Main Protocol – Additional Protocols and Relevant Research

Section 1

Main Protocol:

Feasibility of ischemic leg ulcer healing using percutaneous techniques: a real-life study

Introduction

Lower extremity artery disease (LEAD) is a common disease leading to pronounced morbidity and mortality as well as to consumption of many healthcare and social-care resources. Major risk factors include ageing population, increasing prevalence of diabetes and its lower-limb-related complications, along with tobacco consumption [1–3]. Critical limb ischemia (CLI), the most severe clinical manifestation of LEAD, may present with ischemic foot ulcers, rest pain, and gangrene [4].

Ischemic ulcers often begin as minor traumatic wounds that subsequently fail to heal because the blood supply is insufficient to meet the increased demands of the healing tissue [5]. Furthermore, ische- mic ulceration is potentially associated with increased risk for subsequent limb loss, high healthcare costs, and mortality [4].

Although surgical reconstruction was the standard of care for treating limb-threatening ischemia for nearly five decades, endovascular techniques have become an attractive therapeutic alternative for the majority of ath- erosclerotic lesions in patients with ischemic foot ulcers [6–10]. Moreover, recent data indicate that treatment of CLI patients with an endovascular-first intervention may be associated with lower rates of major adverse cardiovascular events, surgical site infection, bleeding, unplanned reoperation, unplanned readmission,

and, in general, with a substantially lower early morbidity compared to a surgery-first procedure [11].

Therefore, the aim of our study was first to evaluate the technical effectiveness of percutaneous transluminal angioplasty (PTA) in the management of lower limb ath- eromatous lesions in patients with ischemic foot ulceration in a real-life setting. The secondary aim was to assess the clinical effectiveness of PTA, including ulcer healing and amputation-free survival in these patients.

Material and Methods

Study population

We conducted a single-center, prospective cohort, obser- vational study which included patients presenting with ischemic foot ulcers between June 2009 and June 2015. Inclusion criteria were an ulcer in the foot and an ankle-brachial index (ABI) < 0.9 or toe-brachial index (TBI) < 0.7, in case of incompressible tibial arteries at the level of the ankle. The exclusion criteria were: refusal to participate; refusal of PTA therapy; absolute contraindica- tion to contrast media injection as determined by the investigator; uncontrollable coagulopathy; and unwill- ing or unable to provide informed consent or return for required follow-up evaluations. Revascularization was performed by endovascular means whenever feasible after an initial evaluation of all patients. Furthermore, cases in which surgical revacularization was considered as the first-line treatment were also excluded. As previously mentioned, an endovascular approach was always preferred when feasible, irrespec- tive of the classification of the lesion according to the TASC II scheme, apart from cases of a profoundly unfa- vorable anatomic pattern (i.e. total occlusion of the infra-renal aorta and common and external iliac arteries bilaterally, total occlusion of the SFA throughout its length by severely calcified plaques and concomitant extensive atherosclerosis and occlusion of the femoral bifurcation, extensive infra-popliteal occlusion of all three tibial vessels with no run-off in the foot).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written informed consent and ethical approval was granted by our Hospital Ethics Committee.

Patient assessment: data collection

All patients underwent a detailed evaluation that included age, body mass index (BMI), past medical history (including co-morbidities, smoking history, and alcohol intake) previous management, referral, ulcer characteristics, and laboratory investigations. Preoperative evaluation included foot pulses assessment, ABI or TBI, and duplex scanning. The same multidisciplinary team was involved in assessment of all lesions. Physical examination of the foot was performed not only at inclusion, but also regularly during the study by our multidisciplinary team.

If non-invasive parameters suggested LEAD, we performed computed tomography (CT) angiography or digital subtraction angiography (DSA) and arranged the endovascular procedure based on angiographic findings. In cases where diagnostic DSA was performed, endovascular revascularization was carried out during the same session when feasible. Evaluation of the short- and long-term clinical success of the pro- cedure was based on ulcer size and appearance.

Definition of tissue healing time was the time needed for complete epithelialization of ischemic lesions. Local wound care was also used, depending on the character of each lesion. Patients with two or more concurrent lesions were represented by the one with the worst outcome. Patients with three or more ulcers on the same foot were considered as having multiple ulcers. Ulcers were classified as: grade 1 superficial; 2 penetrating to tendon or capsule; or 3 penetrating to bone and joint; and stage C ischemic; or D ischemic – infected; according to the University of Texas Wound Classification

[13]. Patients with worsening ulcers after PTA underwent bypass grafting or amputation. Major amputations were equivalent to non-healed tissue lesions. Patients with non-healed tissue lesions one month before death were considered non-healed.

We identified amputations below the ankle as “minor” and amputations through and above the ankle as “major.” “Limb salvage” was achieved in case of avoidance of a major amputation during the follow-up period.

Technique

The main goal of the angioplasty (defining technical success) was to achieve straight-line flow (SLF) from the aorta down to either a patent dorsalis pedis or distal posterior tibial artery supplying the plantar arch. The definition of technical success also included creation of SLF from the aorta to a peroneal artery that supplies either a patent dorsalis pedis or distal posterior tibial via collateral reconstitution.

All patients received PTA-first as the primary form of treatment. They also received medical therapy for risk factor modification. Hypertension definition included office systolic blood pressure (SBP) values 140 mmHg and/or diastolic BP (DBP) values 90 mmHg. All LEAD patients received statin therapy and target was set according to concomitant co-morbidities (i.e. low-density lipoprotein 70 or 100 mg/dL) in accordance with recent guidelines [14,15]. In a subgroup of patients, autologous platelet-rich plasma (PRP) was used with the results published elsewhere [16]. All angioplasties were performed by two interven- tional radiologists of our department who had 1 and 10 years of experience, at the beginning of the study. Antegrade common femoral access was preferred and performed in all patients who had no or non-significant aorto-iliac disease on Doppler arterial scans. Cross- over femoral or brachial accesses were other possible approaches based on lesion location, body habitus, and physician preference. Intra-arterial unfractionated hep- arin 3000–5000 IU was routinely injected via the vascular sheath at the start of the procedure and intra-arterial glycerine trinitrate 200 lg was adminis-

tered before all tibial angioplasties. Angled or straight 0.035-in. guide wires (e.g. Terumo Corporation, Tokyo, Japan) supported by a standard 5-F straight or curved catheter, were used to cross most femoropo- pliteal lesions, while smaller diameter 0.018-in. guide wires (e.g. V-18 control wire, Boston Scientific, Fremont, CA, USA; Cruiser 18, Biotronik, Zurich, Switzerland) were used to cross infragenicular lesions [17]. Our typical angioplasty strategy was to attempt intraluminal crossing of the stenoses or occlusions using a combination of a 5-F curved catheter and a 0.035-in. straight or curved hydrophilic guidewire (Terumo). In case a subintimal channel was created, we switched our technique and attempted subintimal angioplasty. To facilitate intraluminal crossing of chronic total occlusions, we also used vibrational angioplasty in a subcohort of our patients [18]. This is a method that uses a specially designed hand-held motorized device that produces vibrational motion to a 0.014 or 0.018 guide wire [19–21]. Once the lesions were successfully crossed, our treatment strategy con- sisted of direct stenting of lesions prone to peripheral embolization, such as occlusions or complex stenoses in the aortoiliac axis and acute occlusions in the femoro- popliteal region and primary balloon angioplasty of below-the-knee lesions [17,18,22]. PTA was the preferred technique in the femoropopliteal region and stents were only placed in cases with residual stenosis > 30% or residual dissection that compromised the anterograde blood flow. No stents were placed in the infrapopliteal level. All vascular sheaths were removed 2 h after angioplasty and hemostasis was con-trolled by manual compression for at least 10 min. Antiplatelet therapy was administered in every case using either single or dual drug regimens.

Technical success of the endovascular procedure was accomplished when a residual stenosis < 30% was achieved with antegrade blood flow in at least one distal vessel. Adverse events were classified according to the Society for Vascular Surgery (SVS) reporting standards. Complications were described as mild, mod- erate, or severe and access-related, procedure-related, and systemic [23].

Follow-up

The study was designed to follow up patients for at least two years. However, follow-up stopped when the patients withdrew informed consent or were unable to complete follow-up. Furthermore, patients were recorded as lost to follow-up if no information on them was retrieved after attempt to contact them by telephone.

Post-procedure surveillance included quarterly vascular clinic visits, during which clinical improvement (e.g. wound healing, rest pain) was assessed. Follow-up was terminated in case of death or major amputation; oth- erwise, it continued even after complete ulcer healing.

Statistical analysis

Results are presented as mean standard deviation (SD) for continuous variables, if normally distributed, and as median (interquartile range) if not. For comparisons between groups, a two-tailed t-test for independent samples (for normally distributed data) or a Mann–Whitney U test (for non-normally distributed data) was used for continuous variables and the chi-square test for categorical variables. Correlation coefficients were calculated using the Pearson or Spearman's (for non-normally distributed data) correlation test for all the independent predictors of ulcer outcome. Clinically relevant variables were included as independent varia- bles: age; gender; BMI; smoking history; diabetes mellitus; and other co-morbidities. Only variables found significant were further analyzed. Furthermore, a binary logistic regression analysis model was applied, to assess the ability of the previous variables to predict ulcer healing. P values < 0.05 were considered statistically significant. Data were analyzed using PAWP 17.0 software (SPSS Inc, Chicago, IL, USA).

Results

Patients

A total of 225 patients with ischemic foot ulceration were initially evaluated during the study period. Of them, 12 patients were excluded due to various contra- indications for endovascular treatment. From the 213 remaining cases, 52 patients had a profoundly unfavorable distribution of lesions for an endovascular approach, according to the vascular team's consensus, leaving 161 (76%) patients that underwent percutane- ous procedures. Moreover, 17 patients were lost to follow-up before reaching any of the study endpoints (Fig. 1). Finally, 144 patients were studied, 102 of whom (71%) were followed-up for > 24 months. Baseline clinical characteristics of studied patients are presented in Table 1. Co-morbidities were common with a relatively large proportion of patients having diabetes and hypertension. Median pre-procedural ABI was 0.45 T 0.2.

Procedures

PTA was performed in all 144 patients. Lesion type incidence according to TASC II classification was as follows: 10 Type A; 19 Type B; 72 Type C; and 43 Type D. In 88 patients, PTA was performed in the iliofemoral axis exclusively, in 10 patients in the popliteal/tibial axis exclusively, and in 46 in both levels, with an average of 1.8 procedures per patient. One vessel was treated in 66 cases, two vessels in 45 cases, three vessels in 22 cases, and four vessels in 11 cases. Stent placements were required in 42 cases. Initial technical success was achieved in 141 cases. Technical success by type of lesion was 100% for Type A and B lesions, 98% for Type C, and 95% for Type D lesions. The ABI significantly increased post-procedurally from 0.45 T 0.2 to 0.76 T 0.19, P <0.001.

Complications

Adverse clinical events occurred in 13 patients. One patient developed a retroperitoneal hematoma due to a high puncture, treated with a stent-graft implanta- tion. Five patients suffered an access site hematoma requiring transfusion and six patients developed a pseudoaneurysm at the puncture site treated successfully using

percutaneous thrombin injection (24, 25). One patient in whom brachial access was used developed brachial artery occlusion and underwent emergency surgery. In two patients with failure to cross an occluded SFA a femoro-peripheral bypass was performed and in one patient with iliac-occlusion recanalization fail- ure, a femoro-femoral bypass was done. No patients died within 30 days after intervention.

Vascular re-interventions

Repeat PTA to the initially recanalized artery was per- formed in eight patients during the follow-up period. Eight legs were treated with a surgical bypass after late PTA failure. Presence of heart failure (r= 0.3, P =0.024) and popliteal/tibial PTA location (r =0.2, P=0.033), were significant risk factors for re- intervention.

Amputations

Despite successful recanalization, minor or major amputation was required in 36 cases. Of these, 17 were major and 19 minor amputations. The need for amputation was correlated with the extent of tissue destruction at inclusion (r =0.3, P=0.039). However, all had an excellent healing of the amputation stump without further complications.

Ulcer healing

In total, 98 (68%) patients healed primarily without major or minor amputation. Median time to healing was 18 weeks (range 3–52 weeks) (Fig. 2). Presence of hypertension (r –0.4, P 0.015), coronary artery disease (r=–0.4, P =0.011), and extent of tissue destruction at inclusion (r=–0.9, P < 0.001) were associated with a lower probability of healing.

Multivariate analysis identified only the extent of tissue destruction at inclusion as an independent signif- icant factor for ulcer healing after adjustment for confounders (P < 0.001).

Limb salvage

The overall cumulative limb salvage rate was 88.2% at the mean follow-up time of 3.1 years. The extent of tissue destruction at inclusion ($r = 0.66$, $P < 0.001$) and the need for bypass surgery ($r = 0.3$, $P < 0.001$) significantly increased the risk of major amputation.

Survival

At a mean follow-up of 3.1 T 1.8 years, the survival rate was 69% (44 patients died, 28 of whom from cardiac causes, eight from stroke, four from uncontrolled sepsis, and four from malignancy).

Amputation-free survival: During the follow-up period, amputation-free survival was 64%. Amputation-free survival with healed ulcers: During the follow-up period, 62% of patients had achieved ulcer healing and were alive without a major or minor amputation.

Discussion

Our data support the technical and clinical success of PTA in the management of ischemic foot ulcers with high rates of healing and limb salvage. PTA was technically successful and feasible in almost all patients with only a minority of cases unsuitable for percutane- ous techniques due to extensive and complex distribution of atherosclerotic lesions.

Another important aspect of our study is that most of the patients' lesions were classified as TASC II Type C and D, with 98% and 95% technical success, respectively, indicating that endovascular procedures can be performed in patients to whom surgical inter- vention was previously recommended. Therefore, our results challenge the traditional criteria for recommended treatment and also confirm previous reports [26, 27] regarding clinical utility of the TASC classifica- tion system. Nevertheless, correct patient selection, operative planning performed by a multidisciplinary vascular team, and current advances and improvements in angioplasty tools and skills may have also contrib- uted to our outcomes.

In our study, adverse events occurred in 9% of patients, mainly access-related and peri-procedural mortality was 0%, compared to a roughly

3% mortal- ity rate and 20% major complication rate of infra- inguinal bypass [28–30]. Furthermore, in clinical research, the mortality rate of patients with intermit- tent claudication is 2.5 times higher than age-matched controls, while patients with CLI present a mortality rate as high as 20% the first year after diagnosis [4,10]. Therefore, a less-invasive treatment strategy is prefera- ble to prevent mortality especially in high-risk patients. This was the case in our study population in which, despite the relatively large proportion of diabetes and cardiovascular disease and the lower mean ABI (0.45) compared to previous studies [32], the overall survival rate was around 70% during a mean follow-up of 3.1 years. An 88% overall limb salvage rate and 64% amputation-free survival were observed, which were higher compared to previous studies in patients with LEAD and diabetic foot ulcers who did not undergo revascularization [31,32]. As amputation-free survival is similar to overall survival, we could speculate that the effectiveness and durability of endovascular treatment are probably enough to meet the needs of these patients.

Our study has several clinical implications. As LEAD confers a significantly higher risk for limb loss, compared to other types of ulcers [33], aggressive attempts for revascularization with the use of percuta-neous techniques may have great importance and account for these favorable results. Another important implication of the present study is that secondary inter- ventions after an initial percutaneous approach, either by endovascular or by surgical means, had a high rate of success. In support of this, there are data suggesting that initial therapy with endovascular means does not preclude failure of secondary surgical revascularization and that feasibility of a secondary bypass and limb salvage rates are similar to the primary bypass proce- dure [34, 35]. On the other hand, data from the BASIL trial showed that patients in the endovascular group who needed a secondary bypass fared worse than those originally assigned in the surgical group [36].

However, these results should be interpreted with cau- tion, as the investigators did not focus on the question if an initial percutaneous

procedure resulted in loss of outflow and subsequently precluded a surgical option. Since this was a group of a failed intervention, these cases should probably compare to the group of surgery after a prior failed surgical procedure.

Importantly, the extent of tissue destruction seems to predict worse healing over time. Delay between the onset of a foot lesion and first treatment is common and attributed mainly to underestimation of the severity of foot lesions or lack of recognition of ischemia [37]. Our results underline the need to consider invasive revascularization as early as possible in patients with ischemic foot ulcers, irrespective of the presence of pain or the extent of wound. Unfortunately, assessment for revascularization in patients with ischemic foot ulcers is considered only after failure of conservative treatment [38,39].

This study has limitations that deserve comment. First, it was not a randomized trial and no control group was specified in the study design. Instead, patients served as their own controls before and after PTA. Although a matched control group receiving non-interventional therapy would be desirable for the interpretation of the effectiveness of revascularization, this was not possible due to ethical issues, especially regarding patients with more severe disease and thus possibly increased risk of amputation. Second, the ana- tomical success rate (i.e. vessel patency/restenosis) is not precisely known, because patients who improved hemodynamically and clinically do not routinely receive post-PTA imaging. Clinical evaluation alone was acceptable for clinical outcome, even though the same is not true for technical outcome. Third, wound care was not standardized, which might have influenced ulcer healing time. However, there is no convincing evidence that any wound dressing or local ulcer treatment method is better to promote ulcer healing process. Fourth, owing to the relatively long period studied (June 2009 to June 2015), the population was not homogeneous. Significant technical advances during the study may have biased our results. Obviously, the outcome of PTA versus vascular surgery in the present study is not directly comparable, because, according to the study design, our strategy was

PTA-first with surgical reconstruction reserved for patients not amenable to PTA. Finally, 17 out of the original 161 patients were lost to follow-up (11%). This is an important study limitation, probably due to socioeconomic fac- tors in our study sample. At the time of hospital discharge all patients were alive with no amputation, but unfortunately no further follow-up data were available.

In conclusion, endovascular intervention as the first- line treatment in patients with arterial insufficiency and ischemic foot ulcers is feasible in the vast majority of patients and has a very high technical success rate. Percutaneous revascularization results in a high overall incidence of wound healing and limb salvage, accompanied by very low morbidity and mortality rates. Factors that affect clinical success, potentially affecting optimal treatment strategy are the extent of tissue destruction at presentation, along with patient co-morbidities.

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Section **2**

Additional Protocol 1:

Vibrational angioplasty in recanalization of chronic femoropopliteal arterial occlusions: Single center experience

Introduction

Peripheral arterial occlusive disease (PAOD) is the most common cause of symptomatic obstruction of the human vascular tree, affecting 12–14% of the general population and up to 20% of those over 70 years old [1]. Although the pathogenetic mechanisms that lead to PAOD are similar to those of coronary artery disease, in the peripheral vasculature and specifically in the femoropopliteal segment, chronic total occlusions (CTOs) predominate stenoses [2].

The predominance of CTOs is due to limited collaterals and to the diffuse nature of the disease [3]. Therefore, CTOs are commonly found in patients with PAOD, occurring in up to 40% of symptomatic patients [4]. The presence of CTOs typically results in critical limb ischemia and restrictive intermittent claudication. Various peripheral arterial occlusive lesions (type D and type C lesions in TASC classification) have traditionally been managed with surgical therapy. However, the increased number of patients with multiple comorbidities, severe forms of PAOD and increased surgical risk, makes percutaneous transluminal angioplasty (PTA) a useful alternative to reconstructive surgery in order to minimize potential complications and improve patient outcome [5]. Approximately one-third of femoropopliteal PTAs are currently performed in the setting of

CTOs with an average of 20% procedural failure rate using traditional guidewire and balloon technology [6,7].

The causes of failure are the complexity of these lesions and the difficulty of crossing the site of occlusion with conventional guidewires or the inability to reenter the distal true lumen from a subintimal path. In comparison with simple stenoses and acute occlusions, recanalization of CTOs is associated with lower technical success rates, higher complication rates – such as distal embolization and perforation – longer procedural times as well as elevated radiation dose levels for patients and staff [8].

In order to overcome the challenge of treating peripheral CTOs and improve the safety and effectiveness of percutaneous revascularization, several mechanical devices and techniques have been used. The technical success rates of different methods and devices in CTO's recanalization have a range from 65% to 100% [9–13].

Vibrational angioplasty is a low-energy technique that facil- itates intraluminal navigation of guidewires through resistant lesions, avoiding the damage of the collateral vessels and caus- ing less vascular trauma. Initially it was applied successfully in recanalization of chronic coronary total occlusions [14,15]. Previously 6 patients with long femoropopliteal and 12 patients with infrapopliteal occlusions have been treated with vibrational angio- plasty, with an overall success rate of 100% and 92% respectively [16,17]. However, further studies with larger patient populations are needed to determine the utility of vibrational angioplasty in peripheral CTOs. The aim of this prospective study is to report the overall success rate, safety and the outcome of vibrational angio- plasty technique, in the treatment of chronic total femoropopliteal occlusions in our institute.

Methods

Patients and design

The study population comprised of patients with chronic total femoropopliteal arterial occlusions, which were treated with vibrational angioplasty during the same session after a failed attempt of

conventional recanalization technique. The patients were enrolled in the study from October 2000 to December 2008 in a consecutive order depending on vibrational device availability (the vibrational angioplasty device was only

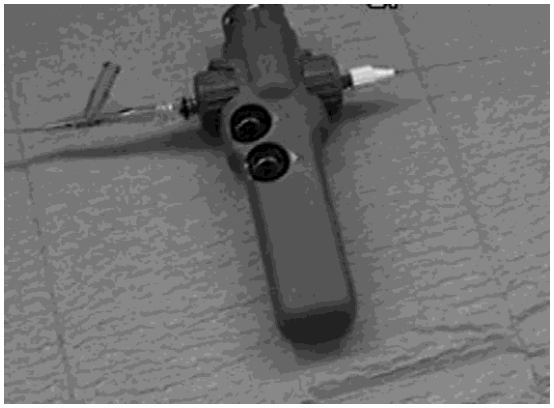

Fig. 1. Vibrational angioplasty device.

intermittently available due to manufacturing restrictions). All subjects provided written informed consent prior to entering the study and ethical approval was granted by our Institutional Review Board. All patients were assessed for risk factors of peripheral vascular disease such as age, sex, smoking, diabetes, hypertension, hyperlipidemia, and renal function. They were also questioned for medical history of coronary artery disease and stroke.

Study inclusion criteria

1. Ischemic rest pain, ulceration, or gangrene (Rutherford category 4, 5 and 6 – Fontaine stage 3 and 4) and/or severe intermittent claudication (Rutherford category 3, Fontaine stage 2) in patients unsuitable for surgical repair due to multiple comorbidities.
2. Angiographically proven chronic total occlusions in the femoropopliteal region.
3. Previous failed attempt to cross the occluded segment with conventional intraluminal techniques that lasted at least 5 min (fluoroscopy time).

Exclusion criteria

1. Contraindication to the administration of iodinated contrast medium.

2. Acute arterial thrombosis.
3. Uncontrolled coagulopathy.
4. At least one subintimal recanalization attempt during which re- entry into the distal true lumen was not achieved.

Pre-treatment angiography

All procedures were carried out in an angiographic suite with a monoplane machine (Artis FC, Siemens, Erlangen, Germany). Intra-arterial Digital Subtraction Angiography (DSA) was performed in order to document and evaluate the location and anatomic char- acteristics of the occlusion. Evaluation included the length of the occlusion, the presence of extended calcifications and bridging col- laterals, the abrupt nature of occlusion stump and the status of distal runoff.

Vibrational angioplasty technique

All procedures were performed percutaneously through an ipsi- lateral antegrade common femoral approach under local anesthesia with lidocaine 1%. Following insertion of a 6 F, 24 or 35 cm long sheath – depending on lesion's level – with its tip close to the occluded segment, 5000 IU of heparin were administrated intra- arterially.

Our typical treatment strategy is to initially attempt crossing the occluded segment intraluminally using a combination of a standard 5 F straight or curved catheter and a 0.035 in. straight or curved hydrophilic guidewire (Terumo). In case the wire creates an unintentional subintimal dissection we switch our technique to a subintimal one.

During the last year we started using dedicated support catheters in combination with 0.014 or 0.018 in. guidewires. In our study population, we decided after 5 min of unsuccessful conven- tional intraluminal attempt to switch to vibrational angioplasty technique.

Vibrational angioplasty was performed by a hand – held motor- ized device, designed to impart vibrational motion to a guidewire in order to facilitate crossing of the occlusion (Fig. 1). The device accommodates guidewires of up to 0.018 in. in diameter and gen- erates a combined reciprocal and lateral movement at the tip of the wire with a range of

frequencies from 16 to 100 Hz. The duration of each activation ranged from 1 to 2 min.

Initially a conventional 0.014 in. coronary guidewire was placed through an over-the-wire balloon catheter (OTW 2.0 mm 20 mm) in order to protrude up to 5 mm from the tip of the catheter and the back end of the wire was connected to the device. The device is able to produce a complex motion at the distal tip of the guidewire, pro- vided that it protrudes slightly from the tip of the balloon catheter. The length of the protruding wire and the frequency of the recipro- cal movement, define the characteristics of the produced motion. A shortly protruding guidewire results mainly in a reciprocal type of movement. This is particularly important, when one tries to brake the hard front of the lesion and enter the occlusion. Furthermore, during activation of the device, the operator exerts a steady forward push on the balloon catheter, in order to facilitate the penetrating effect of the reciprocal ("piston-like") component of the guide-wire movement, while the simultaneous lateral movement produced probes the occlusion for the path of least resistance. After the ini- tial penetration of the guide wire, the protruding tip is increased up to 5 mm, resulting in a more complex movement. This movement facilitates the intraluminal navigation of the guide wire through the occlusion (Fig. 2).

We used progressively stiffer wires i.e., Hunter Soft (Abbott Ireland Vascular Division), Shinobi (Cordis Corp., Miami Lakes, FL, USA), and Crosswire (Terumo Medical Corporation, Tokyo, Japan), depending on the progress of the intervention and the characteris- tics of the lesion. In case of failure of the guidewire/balloon catheter system to progress despite the wire's assumed intraluminal course, the balloon was inflated briefly, and the procedure was contin- ued. Occasionally the 0.014 in guidewire was used just to brake the hard front of the occlusion in order to subsequently facilitate cross- ing of the lesion with a straight 0.035-in. hydrophilic guidewire. This modification of the technique was applied in heavily calcified occlusions in which navigation of 0.014 in. guidewires appeared to be impossible during the initial crossing attempts (Fig. 3).

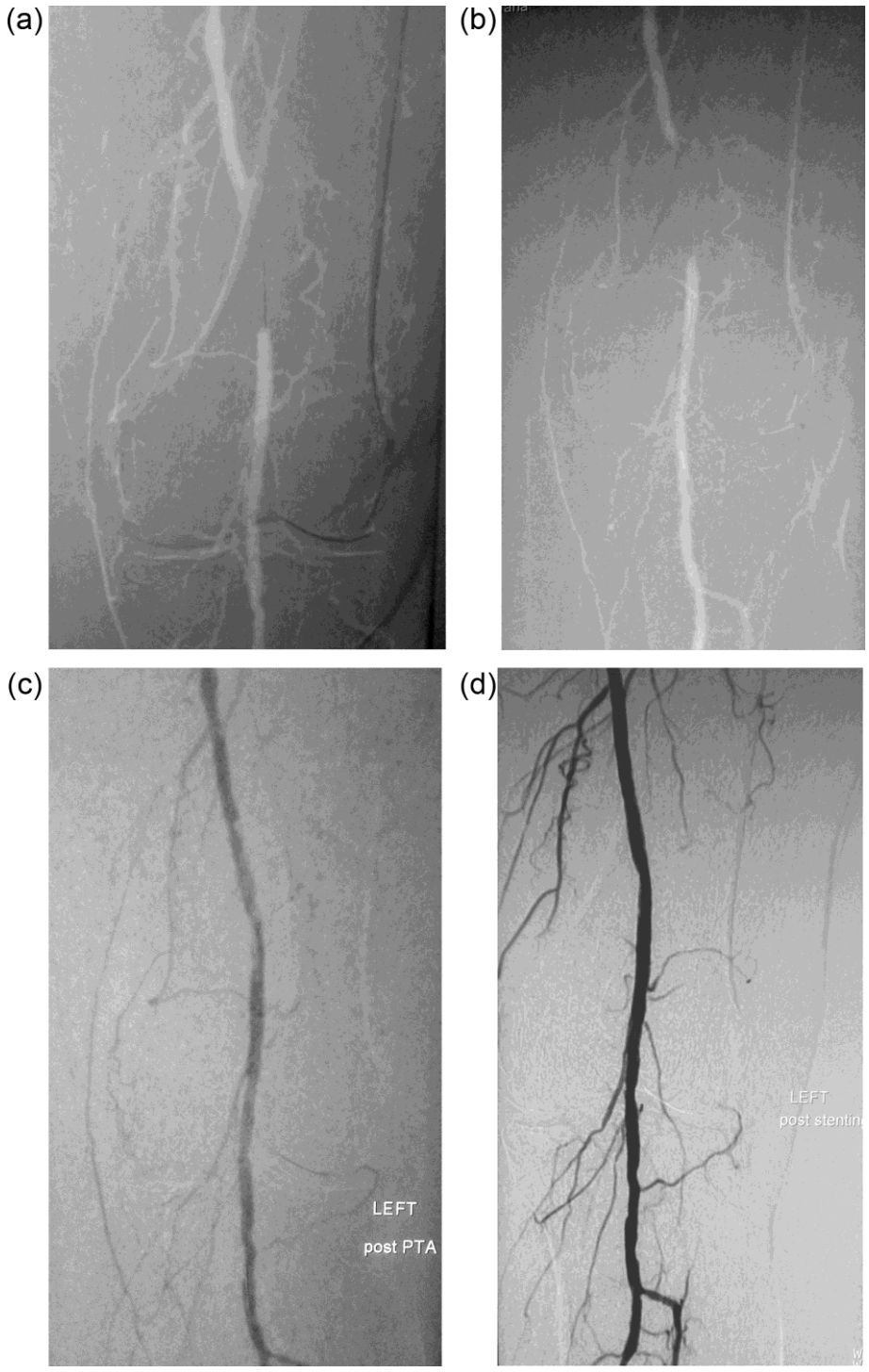

Fig. 2. Seventy-three years old male patient with restrictive claudication and poor surgical risk due to multiple comorbidities. Angiography shows a 4 cm long non-tapered occlusion of the proximal left popliteal artery which surprisingly could not be recanalized with conventional intraluminal technique. (a) The 0.014 in. guidewire tip that protrudes from the 2 mm × 20 mm balloon catheter – both of them attached to the vibrational device – has broken the front of the lesion and has almost crossed the entire occlusion. (b) The guidewire has crossed the occluded segment into the true lumen distally. (c) After balloon angioplasty an intimal flap and residual stenosis observed. (d) Stenting and final result.

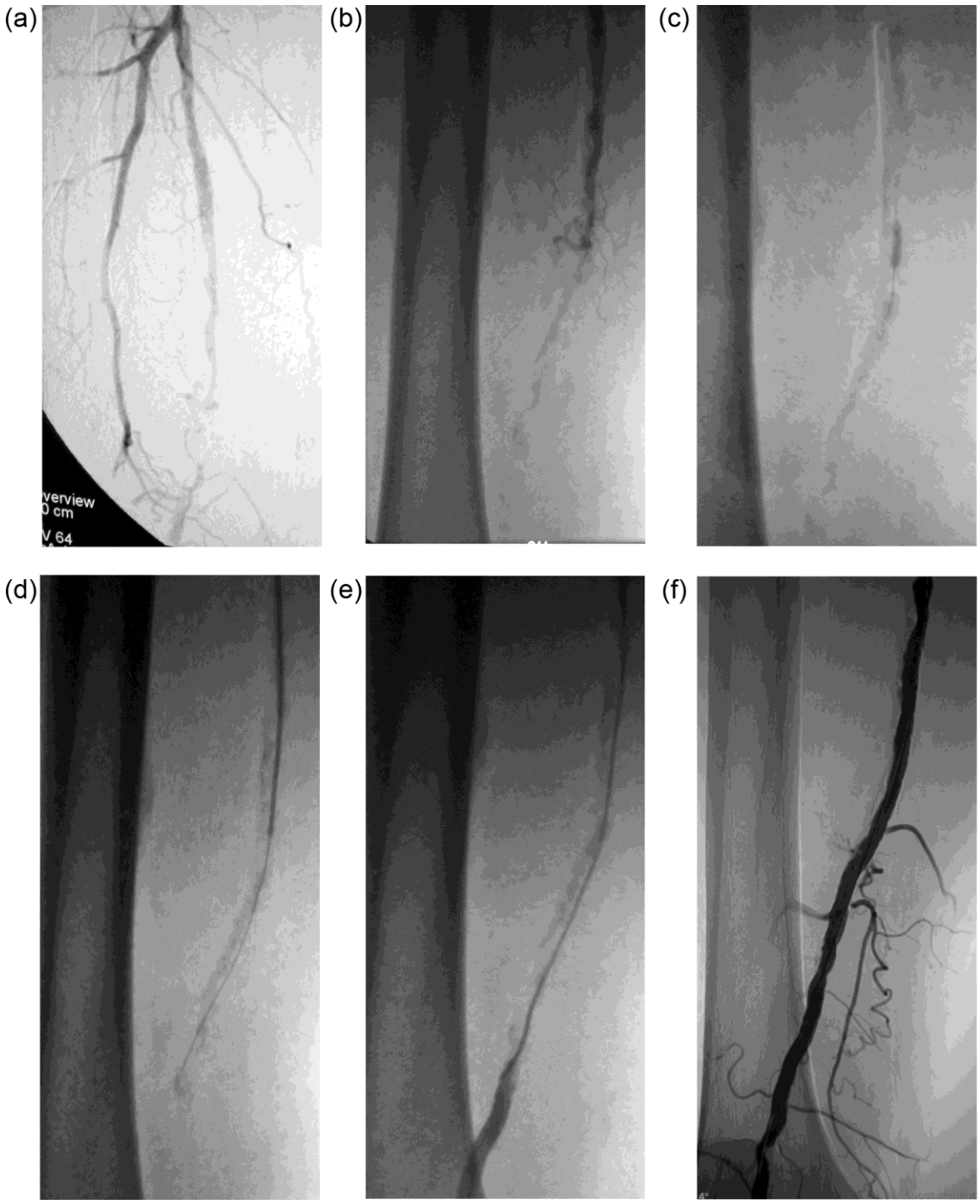

Fig. 3. Male patient with right leg critical limb ischemia. 6 cm long non-tapered occlusion of the distal SFA with heavy calcification (a).

The initial 0.014 in. guidewire supported by the balloon catheter has managed to break the front of the occlusion (b). Subsequently the guidewire failed to navigate into the occlusion after the initial break, despite balloon inflation (c). A straight hydrophilic 0.035 in. guidewire was used in order to facilitate crossing the occlusion (d). The catheter has passed into the true lumen distal to the occlusion (e). Final result following PTA and stenting (f).

After crossing the lesion with the guidewire, contrast medium was injected to document intraluminal position. Following crossing of the occlusion, PTA was performed in the conventional way. No guide or support catheters were used during application of vibra- tional angioplasty technique.

Technical success was defined as complete intraluminal crossing of the occlusion followed by placement of the guidewire into the true distal lumen. Clinical success was defined as dissolution or improvement of disabling claudication symptoms and in cases of critical limb ischemia as limb salvage, ulcer or amputation stump healing and rest pain relief. Minor complications were defined as any adverse event that required no further therapy (e.g., minor groin hematoma). Major complications were defined as any adverse event requiring further therapy or leading to prolonged hospitalization (>48 h) (e.g., retroperitoneal bleeding, pseudoaneurysm requiring thrombin injection) [18].

Follow-up

Patients follow up included serial ankle-brachial index (ABI) measurements and arterial duplex ultrasound examinations at 1, 3, 6, 12, 24, 36 and 48 months. The degree of clinical status improve- ment was assessed using the Society of Vascular Surgery's grading system [19]. Patients with clinical evidence of recurrent disease and typical symptoms of arterial insufficiency were scheduled for control angiography. Amputation-free survival was calculated by Kaplan–Meier life table analysis and is expressed as the percentage of survival probability with standard error.

Results

Twenty-seven patients (16 males and 11 females) and twenty- eight lesions (1 patient underwent a second intervention in a different segment and in a different session on the same limb) were included in our study. Patient's baseline clinical and angiographic characteristics are presented in Table 1.

Table 1
Patient's baseline clinical and angiographic characteristics.

No sex/age (years)	Risk factors	Symptoms	ABI	Arterial location	Length, cm	Ca++	Occlusion stump	Collaterals	TASC II
F/67	DM, HYP, STROKE	Rest pain	Uncompressed	SFA-POPA ak*	10	No	Non-tapered	Yes	B
M/81	CAD, ESRD, HYP, SMK	IC	0.39	SFA mid	6	Yes	Non-tapered	Yes	B
M/74	CAD, DM, HYP	Non healing amputation	0.3	POPA*	3	Yes	Tapered	No	C
M/73	HYP, SMK, HRL	Ulcer	0.4	SFA dist-POPA ak*	8	No	Tapered	No	A
M/75	CAD, DM, SMK	Gangrene	0.19	SFA dist	6	Yes	Non-tapered	Yes	B
F/92	DM, HYP	Ulcer	Uncompressed	POPA-ak	3	No	Non-tapered	No	B
F/61	CAD, SMK, HYP, HRL	IC	0.26	SFA prox	10	Yes	Non-tapered	No	B
M/69	DM, SMK, HYP	Rest pain	0.3	POPA-ak	4	Yes	Non-tapered	No	A
M/52	DM, SMK, HRL	IC	0.6	SFA mid-distal	10	No	Non-tapered	Yes	B
F/83	CAD, DM, HYP	Ulcer	0.4	SFA dist, POPA-	10	No	Non-tapered	Yes	B
M/71	CAD, DM, ESRD, HYP, SMK	Ulcer	Uncompressed	SFA prox	10	Yes	Non-tapered	No	B
F/72	DM, HYP	Ulcer	Uncompressed	POPA ak	6	No	Tapered	Yes	B
F/75	CAD, DM, HYP	Gangrene	0	SFA-POPA ak	8	Yes	Tapered	Yes	B
M/84	DM	IC	Uncompressed	SFA dist	8	No	Non-tapered	Yes	B
M/75	DM, CAD, STROKE	Rest pain	Uncompressed	SFA dist	3	No	Tapered	No	A
M/93	HYP, SMK	Rest pain	0.41	dist SFA-POPA, ak	6	No	Non-tapered	Yes	B
F/80	HYP, HRL	IC	0.32	POPA-ak	4	No	Tapered	No	A
F/77	CAD, DM, HYP	Rest pain	Uncompressed	POPA*	5	Yes	Non-tapered	Yes	B
F/75	DM, CAD, HYP	Rest pain	Uncompressed	POPA-bk	4	No	Tapered	Yes	A
M/73	HYP, SMK, HRL	IC	0.25	POPA-ak	4	No	Non-tapered	Yes	A
M/82	DM	Gangrene	0.2	SFA prox.	6	No	Non-tapered	Yes	B
F/75	DM, CAD	Ulcer	0.2	SFA prox.	10	No	Non-tapered	Yes	B
F/77	HYP, HRL	Gangrene	0.1	POPA	4	No	Non-tapered	Yes	B
M/67	DM, HYP, SMK	Ulcer	0.3	POPA	4	No	Non-tapered	Yes	B
M/53	DM, HRL, HYP, CAD, SMK	Gangrene	Uncompressed	SFA	4	Yes	Tapered	Yes	B
M/57	DM, HRL, CAD, SMK	Rest pain	0.3	POPA	3	Yes	Tapered	Yes	B
M/71	DM, CAD	Ulcer	0.3	POPA	3	Yes	Tapered	Yes	B
M/70	DM, HYP, CAD	Rest pain	0.5	SFA dist-POPA ak	5	Yes	Tapered	Yes	B

CAD, coronary artery disease; DM, diabetes mellitus; ESRD, end stage renal disease; f/m, female/male; HRL, hyperlipidemia; HYP, hypertension; IC, intermittent claudication; POPA ak, popliteal artery above knee; POPA bk, popliteal artery below knee; SFA, superficial femoral artery; SMK, smoking; TPT, tibioperoneal trunk; *, in-stent restenosis.

Twenty-five out of twenty-eight lesions (89.3%) were success- fully recanalized. Eighteen from twenty-four patients (75%) that were recanalized successfully had diabetes mellitus. All three patients that were unsuccessful had diabetes mellitus and two of them had extensive arterial calcification. Failure was due to inabil- ity of the guidewire to break the front of the lesions (10 cm and 8 cm long) in patients with extensive calcification. The third failure case was due to inability of the guidewire to cross the occlusion intraluminally after successfully entering the proximal end (6 cm long occlusion). One patient in whom recanalization failed underwent surgical treatment with femoropopliteal bypass and died a few days later from heart attack. The two other patients with failure underwent amputation. Seventeen lesions had no tapered occlusion stump and twenty lesions had extented bridging collaterals.

In four cases a straight 0.035 in. hydrophilic guidewire (Terumo) was additionally used in order to facilitate crossing of the lesion after breaking the hard front end of the lesion with a 0.014 in. wire. Time to cross the lesion with wire was estimated from 3 to 23 min (average 10.1 min). In all successfully recanalized occlusions no obvious flow limiting dissections were identified, following cross- ing of the lesion by the guidewire and – interestingly enough – after conventional PTA. In eleven patients stent deployment was deemed necessary due to

residual stenosis following PTA. Additional balloon dilatation was performed in five cases in order to improve inflow, or outflow and ensure optimal outcome.

Pain relief was noticed in all six patients with intermittent clau- dication and in eight patients with rest pain. From ten limbs with tissue loss (ulcer or gangrene) in successfully recanalized cases, six healed without major, or minor amputation. One non-healing amputation stump was healed after recanalization, without further complications. Four limbs underwent amputation (one minor and three major) despite successful recanalization, however all had an excellent healing of the amputation stump without further complications.

Vibrational angioplasty results are presented in Table 2. The association of risk factors with procedural outcome is presented in Table 3. The Kaplan–Meier test (Fig. 4) demonstrated 90%, 85% and 70% amputation-free survival rate at 12, 24 and 36 months, respectively. No major or minor complications were encountered.

Table 2
Vibrational angioplasty results.

Technical success	Crossing time	ABI	Pain relief	Amputation	Healing	Additional dilation
Yes	19 min	Uncompressed	Yes	No		SFA before lesion
Yes	12 min	0.85	Yes	No	–	No
Yes	3 min	0.65	Yes	–	Yes	No
Yes	15 min	0.57	Yes	No	Yes	No
Yes	10 min	0.75	Yes	Yes (minor)	Yes	No
Yes	5 min	Uncompressed	Yes	No	Yes	No
Yes	17 min	1.0	Yes	No	–	No
Yes	6 min	0.7	Yes	No	–	No
Yes	18 min	0.8	Yes	No	–	No
Yes	20 min	0.65	Yes	No	Yes	No
No	–	–	Failed	– (Death)	No	–
No	–	–	Failed	Yes (minor)	–	–
No	–	–	Failed	Yes (major)	–	–
Yes	16 min	Uncompressed	Yes	No	–	Yes
Yes	8 min	Uncompressed	Yes	No	–	No
Yes	9 min	0.5	Yes	No	–	No
Yes	6 min	0.45	Yes	No	–	No
Yes	10 min	Uncompressed	Yes	No	–	Yes
Yes	7 min	Uncompressed	Yes	No	–	No
Yes	5 min	0.46	Yes	No	–	No
Yes	12 min	0.2	–	Yes (major)	Yes (stump)	No
Yes	23 min	0.6	Yes	No	Yes	No
Yes	5 min	0.7	–	Yes (major)	Yes (stump)	No
Yes	5 min	0.85	Yes	No	Yes	Yes
Yes	8 min	Uncompressed	–	Yes (major)	Yes (stump)	No
Yes	3 min	1.0	Yes	No	–	No
Yes	4 min	0.7	–	No	Yes	No
Yes	7 min	0.7	Yes	No	–	Yes

Table 3
Risk factor association with procedural failure.

Risk Factors	*N* (all patients)	%	*N** (failed-3pts)	%	*p*-Value
CAD	15	55.5	2	66.6	NS
DM	20	74.0	3	100	NS
SMK	12	44.4	1	33.3	NS
HYP	20	74.0	3	100	NS
HRL	8	29.6	0	0	NS
ESRD	2	7.4	1	33.3	NS
STROKE	2	7.4	0	0	NS

NS, non-significant.

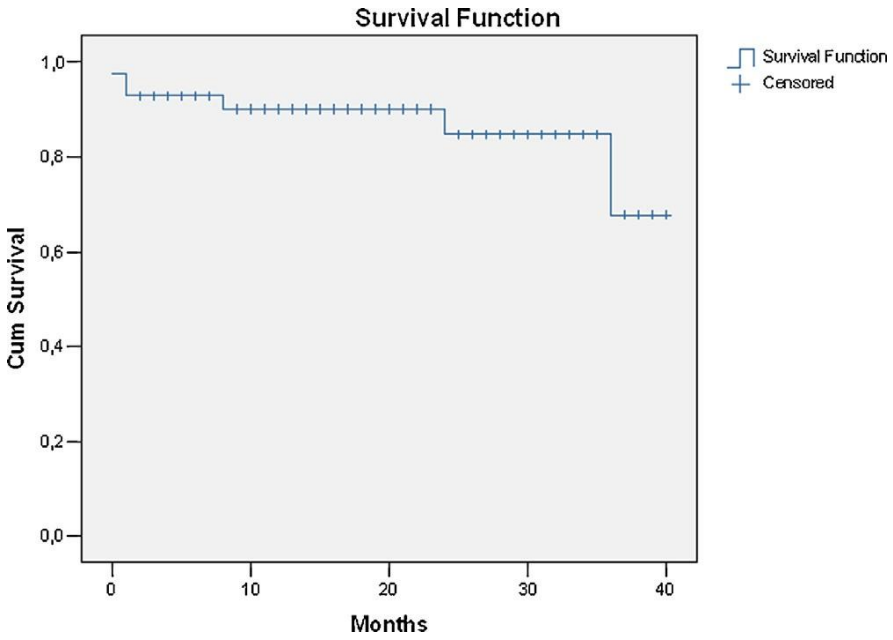

Fig. 4. Kaplan–Meier test showing amputation-free survival rate.

Discussion

Femoropopliteal segment is a common, challenging to treat, region of chronic total occlusive lesions. As CTOs account for a sig- nificant portion of the lesions encountered by interventionalists and one of the primary causes of procedural failure in peripheral interventions, there are concerns about the ability to recanalize safely and the long-term durability of therapy. The two ways to address CTOs currently is either intraluminal or subintimal approach, a choice that is highly dependent on personal training and expertise. Both procedures are low cost options and can provide effective CTO crossing with acceptable technical success rates [20]. Conventional catheter-supported guidewire manipulation is the most commonly used intraluminal CTO crossing method: however, it is associated with high rates of procedural failure and may require conversion to subintimal technique to achieve a technically suc- cessful crossing. In addition, it is almost impossible to know if the guidewire remains in the true lumen along entire CTO course and because of the amount of intraluminal material, adjunctive therapy may be required to debulk or modify plaque [21,22].

For conventional intraluminal CTO recanalization, a variety of guidewires (straight or angled tip configuration, full-length or only distal tip hydrophilic coating, variable tip loads, soft or stiff) are generally used with variable diameter (0.014–0.035-in.) and length (180–300 cm) depending on the point of access, operator preference, amount of calcium and the need for adjunctive tibial recanalization. The guidewires are supported by conventional standard or hydrophilic 4–5Fr catheters with various tip configu- rations. Recently introduced dedicated CTO support catheters have been successfully used in combination with matching guidewires of variable diameters.

Subintimal recanalization, developed by Bolia and Bell [23], is an accepted method in the treatment of CTOs with high technical success rates and high limb salvage rates in critical limb ischemia, but advanced interventional skill is required and there may be a 10–15% need for a reentry device and a substantial need for adjunctive stenting [24]. Furthermore, subintimal angioplasty carries a significant risk of collaterals damage. Collaterals comprise a phys- ical bypass to the ischemic tissue. The combination of collateral thrombosis and the inability to re-enter into the distal true lumen can be disastrous and lead to limb loss. As a consequence many interventional centers, including ours, favor intraluminal approach as the first choice in recanalization of CTOs.

During the last decade many different techniques and devices, either intraluminal or extraluminal have been developed for the treatment of CTOs [9,25]. Devices such as the Crosser (Bard Periph- eral Vascular, Inc., Tempe, AZ USA), Frontrunner XP (Cordis Corp., Miami Lakes, Florida, USA), Wildcat (Avinger, Redwood City, CA), SafeCross Radio Frequency (Spectranetics Corporation, Colorado, USA) and Excimer Laser Angioplasty (Spectranetics Corporation, Colorado, USA), have been specifically designed to consistently recanalize CTOs by the intraluminal way. The Pioneer Catheter (Medtronic Vascular) and the Outback Catheter (Cordis) are typ- ically extraluminal devices. As it is almost impossible to be competent and really comfortable with all of the crossing devices in the market, it is

likely that interventionists will continue to use the technique they consider most efficacious based on their own experience. Many of these methods have been shown to be safe and effective in crossing CTOs. Nevertheless, it is still not clear if a specific technique, or device affects patency, or limb salvage rates. No approach has proven superior over the others until now [8].

Vibrational angioplasty, a technique initially presented in 1993 [26] is an effective, user-friendly method that facilitates the passage of a guide wire through the real lumen, in order to avoid subinti- mal dissection of the arterial wall. This is achieved by a combined reciprocal and lateral movement of a low profile guidewire, slightly protruding from the tip of a balloon catheter, a movement produced by a hand-held external generator. It was first studied in an animal model, with greater crossing success and no perforations compared to manual wire manipulation [27]. The effectiveness and safety of the method has already been demonstrated in difficult chronic coronary occlusions [15,28], with higher crossing success and less severe dissections than conventional hydrophilic guidewires [28]. Interestingly enough, only 1 perforation (without clinical consequences) has been encountered so far in all clinical studies in which this method was applied. The lower degree of vessel trauma could be explained by the nature of vibrational movement of the wire which results in more frequent but less severe contact between the wire and the vessel wall because each individual contact time is very short; this theory is supported by the less extensive and less severe damage caused by a vibrating guidewire versus conven- tional guidewire manipulations in normal sheep coronary arteries [29]. The advantage of this method is that the intraluminal course avoids the risk of bridging collaterals thrombosis and produces less wall trauma than the subintimal passage. Furthermore, vibrational angioplasty, as a low energy technique in combination with low profile guidewires can avoid extended wall injury that may lead to higher rates of hyperplasia and restenosis.

The preliminary results of this technique in a group of patients with femoropopliteal and infrapopliteal CTOs were promising [16,17].

Initially, vibrational angioplasty was applied to successfully recanalize chronic total occlusions in the SFA or popliteal artery in 6 patients, with no complications and a follow up ranging from 3 to 9 months, during which time all arteries were patent on duplex ultrasound imaging [16]. After the positive preliminary results the method was applied in thirteen patients with chronic total occlu- sions. Twelve of these patients were successfully treated and one failed because of wall perforation with no long-term clinical sequelae [17]. The follow up in this study ranged from 1 to 18 months, during which time none of the patients experienced hemodynamic deterioration.

The present study includes a larger number of patients and longer follow-up time, demonstrating the efficacy as well as safety of vibrational angioplasty technique in the treatment of CTOs. There were no major complications and no angiographically visible trauma, or dissection was noticed. As it results from the relevant Kaplan Meier curve, vibrational angioplasty is a method with sig- nificant contribution in amputation free survival of the patients with critical limb ischemia. This is of great importance, because amputations result in increased rates of morbidity and mortality, increased cost and poor quality of life. As most of these patients have decreased life expectancy, it is obvious that the extension of free amputation time may offer them a free amputation life. In our study, only 4 patients needed amputation despite successful recanalization, but they ultimately had a complete and uncompli- cated healing of the stump.

Our study has some limitations that deserve comment: first, the sample size was relatively small, because the vibrational angioplasty device was only intermittently available due to manufacturing restrictions. Second, the study population was non- randomized, and no control group was specified in the study design. Third, the mean lesion length was relatively short, due to the fact that we included a considerable number of popliteal lesions < 5 cm in length in whom we were reluctant to insist on recanalization by conventional techniques due to the fear of a disastrous dissection. Lastly, since we tried this technique only in cases in which an initial intraluminal attempt by

conventional means failed, we cannot evaluate the real success rate of this technique in de novo patients.

In conclusion, vibrational angioplasty is a safe, effective and durable endovascular technique for the treatment of chronic femoropopliteal total occlusions in patients that would be difficult to recanalize using conventional techniques.

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Section 3

Additional Protocol 2:

Effectiveness of Platelet-Rich Plasma to Enhance Healing of Diabetic Foot Ulcers in Patients With Concomitant Peripheral Arterial Disease and Critical Limb Ischemia

Introduction

Diabetes is a major health problem that is currently showing an alarming rise in its prevalence. This has recently been estimated at 7.8% in the United States, presenting a >50% increase over the past 15 years while there exists a large population group in whom diabetes is undiagnosed [1]. Diabetic foot ulceration (DFU) is an unavoidable event during the clinical course of many patients, up to 25% of whom will suffer from a foot ulcer during their lifetime [2]. Approximately 20% of these ulcers ultimately require amputation and 85% of all diabetic lower limb amputations are preceded by an ulcer.2 It is worth noting that these patients are 15 to 30 times more likely to undergo an amputation than those without diabetes [3, 4].

The pathophysiology of DFU lies on the mixed effects of sensory, motor, and autonomic neuropathy along with abnormal foot mechanics, structural deformities, microvas- cular angiopathy, and compromised immune system. The aforementioned factors often coexist with peripheral arterial disease (PAD), which compromises perfusion on a macrovascular level having a substantial deteriorating effect and indicating a worse prognosis[5,6]. The true prevalence of PAD in diabetic patients has been difficult to deter- mine because pain

perception may be blunted in many of them while others due to a poor general status undertake only minimal physical activity in their daily practice, which is not enough for ischemic symptoms to develop. Accordingly, diabetic patients with PAD are more likely than nondiabetic patients to present advanced disease at initial diagnosis, often with an ulcer and critical limb ischemia (CLI) as the first symptoms [7]. In many modern series, a high prevalence of diabetes among subjects undergoing revascu- larization for limb salvage is reported ranging from 50% to 80%. This was 58% in the BASIL trial, 64% in the PREVENT III trial, and exceeds 70% to 80% in many specialized vascular centers [8-13].

To maximize potential for wound healing, a multidisciplinary approach is needed, involving off-loading, regular wound debridement, ultimate control of gangrene or sepsis, antibiotic therapy, negative-pressure wound therapy, and sometimes skin grafting, while glycemic control is of paramount importance. However, these therapeutic measures can succeed only in the presence of adequate arterial perfusion. Subsequently, aggressive attempts for revasculariza- tion are indicated as one of the first and most important measures to enhance ulcer healing and maximize possibilities for limb salvage [14]. Therefore, endovascular and surgical techniques are being employed in this regard, to provide adequate blood flow and restore oxygenation in an effort to allow inflammatory and proliferative tissue response, nec- essary for ulcer healing to take place. Nevertheless, it is not rare that these patients are not suitable for such interventions since the unique anatomy of occlusive disease in dia- betic patients, which mainly involves arteries distal to the popliteal, sparing more proximal segments of the arterial tree, often precludes any kind of revascularization. Unreconstructable vascular disease has become the most common indication for primary or secondary amputation, accounting for nearly 60% of patients [15]. Moreover, a sig- nificant proportion of patients with diabetes may present significant comorbidities, thus not being good surgical candidates to undergo lengthy, complex, and repetitive surgical procedures. Therefore,

restoration of arterial perfusion is not always an option and in this scenario amputation is a frequent outcome.

The use of growth factors (GFs) as an adjunct to enhance tissue remodeling and promote ulcer healing has been extensively studied in the literature. The rationale for their use lies on their contribution on the biological events that take place during the healing process [16,17]. Various research studies have suggested a therapeutic potential of externally applied GFs in patients with impaired wound healing gener- ally by achieving better healing rates, reducing ulcer volume and area, and decreasing time to complete healing [18-25]. Nevertheless, studies investigating the possible gain of such interventions generally have treated lower limbs with adequate arterial perfusion, having excluded those with PAD, which, as mentioned previously, can be the case in a signifi- cant proportion of this population [24-26]

In the current study, we attempted to examine the effi- cacy of autologous platelet-rich plasma (PRP) for the treat- ment of DFU in patients with concomitant PAD. Subjects in the most severe spectrum of arterial disease, meaning those with CLI, were also included. In this regard, our research aims to investigate whether GFs could also serve as a useful adjunct for ulcer healing in patients with diabetes and concomitant unreconstructable arterial disease or those who would not be good surgical candidates and otherwise would most likely have ended up with a major amputation.

Methods

Study Design

This is a single-center, retrospective study including patients treated during a 24-month period from May 2009 to April 2011. Institutional review board approval was obtained for the current study. Eligible subjects were those meeting the following inclusion and exclusion criteria.

Inclusion Criteria

• Type 1 or 2 diabetes controlled by either medication or insulin.

• Presence of a foot ulcer for at least 4 weeks to be considered chronic.

• Diabetic foot ulcers that are clinically noninfected. A culture was obtained but generally infection was diagnosed through clinical signs and symptoms [27].

• According to University of Texas Treatment-Based Diabetic Foot Classification System ulcers with wound depth 0 (pre-ulcerative lesion or healed ulcer site), 2, and 3 (wound extends to tendon, bone, or joint) were not included as well as those of class A (− Infection, − PAD), B (+ Infection, − PAD), and D (+Infection, + PAD). Ulcers of grade 1C were included (Wounds without tendon, capsule, or bone involvement, − Infection, + PAD) [28].

• Presence of PAD as defined by an ankle–brachial index (ABI) <0.9. In patients with falsely elevated ankle pressures due to incompressible vessels at the level of the ankle, the toe–brachia index (TBI) was used and PAD was indicated by a TBI <0.7.15 To measure ABI a 10- to 12-cm sphygmomanometer cuff is placed just above the ankle and a Doppler instrument is used to measure the systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg. These pressures are then normalized to the higher brachial pressure of either arm [15].

The precise level of perfusion deficit that defines “critical ischemia” is unclear especially among patients with diabetes [29]. Nevertheless, for simplicity reasons we followed the TASC II document classification to perform the current analysis. Therefore, patients with an ankle pressure >70 mm Hg or toe pressure >50 mm Hg for those with incompressible vessels at the level of the ankle were assigned to group A, while if ankle pressure was <70 mm Hg or toe pressure <50 mm Hg, subjects were considered to suffer from CLI and they were assigned to group B. To those patients that surgical revascularization or endovascular procedures were indicated and were feasible these had been undertaken before initiation of PRP application. Median time interval from reperfusion to initiation of treat- ment with GFs was 21

days. Subjects included in the current analysis were judged unsuitable for any additional revascular- ization to be attempted. This was mainly due to multilevel, dif- fuse atherosclerotic disease, in the absence of distal run off vessel for arterial bypass to be feasible.

Procedures

General Measures. In both groups, wounds were initially cleansed with normal saline and moist saline gauze dress- ings were used. Cleansing with normal saline solution was performed gently using gauzes and/or sponges with mini- mum mechanical force. When required, patients had surgi- cal debridement of the wounds before application of GFs to freshen the wound bed and remove all necrotic tissue. Cul- tures were taken at that time. All patients were advised to undertake offloading in order to relieve pressure on ulcers. This was always performed using therapeutic shoes or in- shoe orthoses, while casts and/or surgical offloading was not used in any case in this series. There is a general consensus regarding use of footwear and offloading techniques for the prevention and healing of plantar foot ulcers in diabetic patients by reducing plantar pressure at sites of ulceration. The mechanical effect of special footwear is thought to rely on plantar pressure reduction over the at-risk area and a transfer of load to other regions.

To relieve pain, usually oral paracetamol was prescribed with the addition of opioids (drops tramadol) when the patient could not tolerate pain, while need for analgesics tended to decrease along with ulcer healing. Overall, any type of analgesics were required in less than half of our patients, which is believed to be due to reduced pain percep- tion in diabetic patients with severe sensory deficit.

Taking into account that subjects included in the current study by definition suffered from PAD, all patients were on antiplatelet agents. Usually, single antiplatelet regimens with aspirin were preferred while clopidogrel was also used in some instances (ie, allergic reactions in aspirin as a single therapy or dual antiplatelet therapy on patients with

recent cardiac interventions). Statins were also prescribed in the majority of cases.

Exclusion Criteria

- Purulent ulcers with severe infection and wet gangrene
- Exposure of bone, muscle, ligaments, or tendons
- Charcot's arthritis

Patients were divided into 2 groups based on the severity of PAD. Those without CLI were assigned to group A (Fontaine classification stages I, IIa, and IIb) while those with CLI were assigned to group B (Fontaine classification stages III and IV).15

PRP Preparation and Application

- The RegenKit-ATS (RegenLab, Le Mont- sur-Lausanne, Switzerland) system was used for autologous PRP preparation. This contained one safety-lock butterfly needle, one collection holder, the RengenATS tubes and a pair of sterile pliers.
- Two to 4 tubes were filled with the patient's venous blood depending on the ulcer size. The vacuum within the tube enabled automatic collection of the necessary volume of blood (about 8 mL for each tube).
- The blood tube is then immediately centrifuged for 8 minutes to 3000 rpm, which allows blood separation into 2 layers, namely, bottommost red blood cell layer (55% of total volume) and topmost PRP plasma layer.
- After the centrifugation plasma was allowed to clot ex vivo to form a platelet-rich fibrin clot. If the for- mation of the clot is not immediately observed the tubes were kept standing and let to rest for a few minutes (usually 3-5 minutes).
- The sterile pliers included in the set were then inserted to the base of the clot along the tube walls. With a circular movement of the pliers against the wall, the clot was carefully unstuck and extracted.
- PRP is then applied on the ulcer area.
- A small amount of plasma (1-2 mL) was usually pre- sented into the tube after removing the PRP, which was mainly in a semiliquid condition compared to the previously removed PRP gel. This was also

placed on the bed of the ulcer using a sterile syringe. The bottommost red blood cell layer is then discarded.

• Then the area was covered with a moist saline gauze dressing.

PRP application was performed twice a week. Length and width measurements were performed at each visit and area was calculated from these measurements (Length × Width). Photos of the ulcer were taken with a digital camera at that time. Therapy was discontinued either after complete ulcer healing, application of PRP for 16 weeks, or if no or very low progress was observed after 3 continuous sessions. The aforementioned preparation and application of PRP has been previously described with some modification in the literature [30,31] There were no complications from applica- tion of GFs observed in this series.

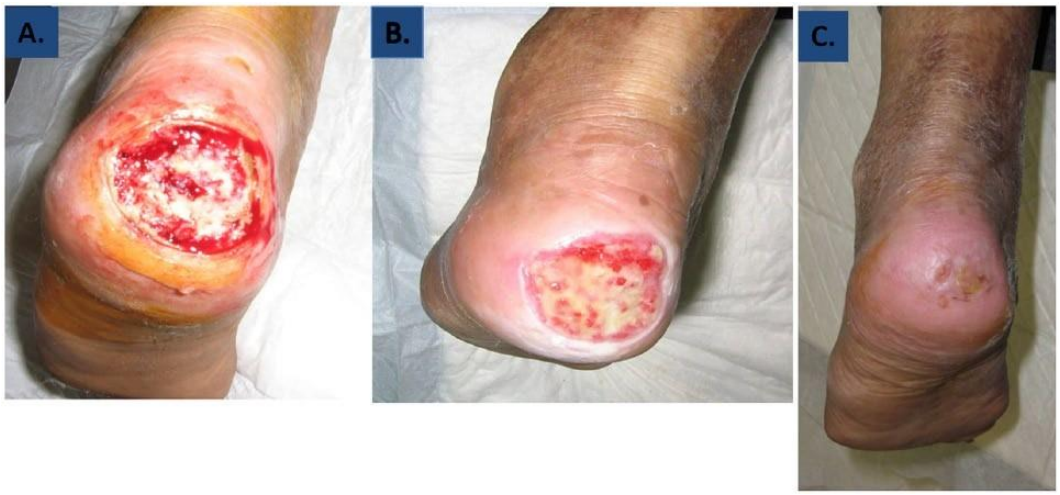

Figure 1. A representative case of foot ulceration in a diabetic patient being assigned to group A (compromised arterial perfusion without CLI). (A) Initial presentation, (B) After session 6, (C) Complete wound healing after session 15.

Endpoints and Statistical Analysis

The main endpoints of the current analysis were ulcer heal- ing or improvement, avoidance of an amputation, and limb salvage.

With regard to clinical outcome, ulcers were characterized as follows:

1. Significantly improved ulcers (ulcer area reduced>90%)

2. Moderately improved ulcers (ulcer area reduced 50% to 90%)
3. Nonimproved ulcers (ulcer area reduced <50%)

Limb salvage according to “Recommended standards for reports dealing with lower extremity ischemia” is applied to therapeutic outcome of interventions intending to avoid a major amputation. The designation “minor amputation” would require retention of a functional foot remnant to allow standing and walking without a prosthesis, which would include toe or transmetatarsal amputations, with most high forefoot amputations as well as below and above knee amputations being included under “major amputa- tions” and fall out of the definition of limb salvage [32].

The aforementioned endpoints were assessed for all patients under evaluation. Rates of ulcer healing, avoidance of an amputation, and limb salvage were recorded for our study population as a whole. Moreover, the same variables were assessed for groups A and B. Statistical significance of differ- ences between groups was evaluated using $\chi 2$ test.

Results

Patient Characteristics and Overall Data

Overall, 72 patients were eligible to be included in the current analysis. There was no loss to follow-up for the patients included in the current analysis. Although majority of cultures obtained from the wound during patient’s initial presentation indicated the presence of microorganisms, mainly aerobic gram-positive cocci particularly staphylococci species and scarcely aerobic gram-negative bacilli and anaerobes, most of this is believed to be colonization since it has been suggested that the presence of infection should be primarily determined on the presence of clinical findings.27 Despite the fact that some debridement was ini- tially required in the majority of ulcers treated in our series (57/72% to 79%) this was always minor.

According to ankle and/or toe pressure measurements, 42 subjects were assigned to group A and 30 patients to group B. Mean age was

65 years and there was a male-to-female ratio of 4:1. Regarding group A, mean systolic blood pressure at the level of the ankle was 98 ± 18 mm Hg and mean ABI was 0.75 ± 0.13. Corresponding values for group B were 48 ± 8 mmHg and 0.35 ± 0.09. Baseline mean ulcer area of all the 72 patients included in the current analysis was 4.1 ± 3.9cm2 (mean ± standard deviation).

Overall, the ulcer was signifi- cantly improved (ulcer area reduction >90%) in 52 patients (72%) within an average of 11 ± 4 sessions. A representative case of complete ulcer healed is presented in Figure 1. In 6 (8%) of our patients the ulcer was moderately improved (ulcer area reduction between 50% and 90%) within an average of 12 ± 4 sessions. In 14 (20%) of the patients there was no benefit from therapy and subsequently they underwent 6 minor and 8 major amputations (20% amputation rate). Limb salvage (avoidance of a major amputation) was achieved in 64 out of 72 limbs treated (89%).

Comparisons Between Groups

Debridement was initially required in 34/42 (81%) patients in group A and in 23/30 (77%) in group B. Since initial debridement was always minor, it did not affect observed results as expected. Comparison of baseline mean ± stan- dard deviation ulcer area between groups A (4.2 ± 3.9 cm2) and B (3.8 ± 3.5 cm2) indicated nonsignificant differences (P = .82). With regard to clinical improvement (ulcer area reduction >50%), there were 36/42 (86%) improved ulcers in group A and 22/30 (73%) in group B, and this difference was not statistical significant (P = .23). Rate of ulcer area reduction >90% was significantly higher in group A (35/42% to 83% vs 17/30% to 56%, P = .02). Regarding need for an amputation, there were 6/42 (14%) amputations in group A and 8/30 (27%) in group B, and the difference was not again statistically significant (P = .23). Finally, regarding rate of limb salvage there was no limb loss in group A (limb salvage 42/42, 100%) and 8 limb losses in group B (limb salvage 22/30, 73%). Limb salvage was sig- nificantly greater among patients in group A (P < .001). These results are summarized in Table 1.

Table 1. Overall Results and Comparisons Between Groups Are Presented[a].

	Ulcer Area Reduction >50%	Ulcer Area Reduction >90%	Any Amputation	Limb Salvage
Group A (n = 42)	36 (86%)	35 (83%)	6 (14%)	42 (100%)
Group B (n = 30)	22 (73%)	17 (56%)	8 (27%)	22 (73%)
Statistical significance	*P* = .23	***P* = .02**	*P* = .23	***P* < .001**

[a]The third column (Any Amputation) refers to both minor and major amputations (nonsignificant differences between groups A and B). The fourth column (Limb Salvage) refers to the avoidance of a major amputation while minor amputation would qualify for limb salvage (limb salvage significantly more common in Group A). Although limb salvage and ulcer healing >90% are significantly more common in group A, results in group B may also represent a quite favorable outcome for these patients. P-values in bold characters indicate statistical significant differences.

Discussion

Diabetic foot ulcers represent a major cause of morbidity between diabetic patients that can seriously impair quality of life and often result in limb loss. GFs have been sug- gested to be a useful adjunct in order to achieve ulcer heal- ing in these patients. These are biologically active polypeptides that act to alter the growth, differentiation, and metabolism of target cells stimulating cellular proliferation, chemotaxis, and angiogenesis [33].

The potential benefits of GFs in the treatment of chronic wounds have been suggested by many investigators. Saad Setta et al performed a randomized trial to compare the effects of platelet-rich and platelet-poor plasma (PRP and PPP), respectively, in ulcer healing demonstrating that this was significantly faster in the PRP group [30]. Anitua et al mea- sured the mean percentage of ulcer surface area healed in their study population, which was 72.94% in patients treated with GFs versus 21.48% in those receiving standard care, a difference that was statistically significant [31]. Steed studied the effects of topical recombinant human platelet–derived GF compared with placebo. They included 118 patients and suggested that the group treated with GFs achieved a significantly higher healing rate (48% vs 21%) while the median reduction in wound area was also significantly greater in the former group (98.8% vs 82.1%) [20] Wieman et al indicated that becaplermin significantly increased the incidence of complete wound closure when compared with placebo and decreased the time to achieve complete wound closure in a study of 379 patients [21] Data from randomized trials suggest amputation rates as high as

45% in patients with DFUs when treated with a standard care protocol while this was signifi- cantly less (15%) for those treated with GFs. These results are broadly similar with those presented in this report (over- all amputation rate 19%) despite the fact that unlike previous research we evaluated patients with concomitant PAD [19]. Others report complete healing rates of only 35% for dia- betic patients receiving standard care, indicating an overall unfavorable prognosis for these lesions.21 Moreover, a recent randomized trial found a quite similar healing rate (81.3%) when compared with our results (72%) for patients treated with PRP in the same time that significantly fewer patients in the control group (42.1%) presented complete wound healing [25].

The above-mentioned studies indicate the effectiveness of local application of GFs to promote tissue repair and enhance ulcer healing. Nevertheless, they all have excluded patients with PAD. In the current study, we concentrate on this particular subpopulation of diabetic patients since they may face a worse prognosis and a higher possibility for an amputation. Our findings indicate good results of PRP regarding ulcer improvement in subjects with PAD. An overall >90% ulcer area reduction was achieved in 72% of patients, which reached 56% in those with CLI (group B). Improvement of the ulcer, meaning >50% reduction in the ulcer area, was achieved in 80% of our study population, while the corresponding value for group B was 73%. Limb salvage was 100% in group A, which was significantly higher than that of 73% in group B. Nevertheless, a 56% rate of significantly improved ulcers and a 73% limb salvage rate in patients with CLI probably represent a quite favorable outcome. As mentioned before, it should be emphasized that mean systolic blood pressure at the level of the ankle was 48 mm Hg and mean ABI 0.35 in this group of patients. These data allow to suggest not only a signifi- cant positive effect of PRP to enhance DFU healing, but also its effectiveness in patients with compromised arterial blood flow.

The present results should be evaluated in light of some limitations, which mainly regard the fact that the analysis was retrospective and it

did not include a control group. Nevertheless, the fate of subjects with diabetes and foot ulceration is mostly well-defined since there is a consider- able amount of information in the literature indicating an overall unfavorable prognosis for these patients [2-4]. More important, fate of the limb of diabetic patients with unre- constructable arterial disease has also been evaluated and limb salvage as low as 54% during 1-year follow-up have been suggested [34]. Therefore, our results being viewed in light of previous large-scale epidemiologic studies allow for meaningful conclusions to be drawn even if we did not include a control group.

In conclusion, PRP is an effective adjunct to enhance would healing and increase limb salvage in diabetic patients with concomitant PAD. Limb loss is significantly higher in diabetic patients presenting with CLI compared with those without and therefore revascularization should be attempted in the former group. Nevertheless, GFs may be used even in patients with CLI to assist treatment of foot ulceration.

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Section **4**

Relevant Research 1:

Direct Stenting in Patients with Acute Lower Limb Arterial Occlusions: Immediate and Long-Term Results

Introduction

Acute lower limb ischemia (ALLI) represents a quickly developing or sudden decrease in limb perfusion, resulting in a potential threat to the viability of the extremity [1]. The hypoperfusion also impairs cardiopulmonary and renal function due to systemic acid–base and electrolyte abnormalities [2]. Causes of ALLI include acute thrombosis of a limb artery or bypass graft, embolism from the heart, dis- section, and trauma [3]. A limb-threatening ischemic event is characterized acute if the duration of symptoms is less than 14 days, subacute between 15 days and 3 months, and chronic after 3 months [4]. A patient with ALLI often presents with the ‘‘5 P’s’’ of paresthesia, pain, pallor, pulselessness, and paralysis, and the incidence is about 1.5 cases per 10,000 persons per year [5]. Patients with ALLI have poor short-term outcomes, with a risk of amputation between 10 and 30% and a mortality rate of approximately 15–20% in the first year, mainly in the peri-operative period[1,6].

The management includes either surgical procedures [7–10] or percutaneous endovascular procedures such us catheter-directed thrombolysis, manual aspiration thrombectomy, and mechanical thrombectomy [4, 11–14]. Surgical revascularization is the classic treatment and includes procedures such us embolectomy with a Fogarty catheter, bypass grafting, and endarterectomy [3]. Despite there is no significant difference in limb salvage rate or mortality

between surgical procedures and catheter-di- rected thrombolysis [8], surgical procedures are associated with higher incidence of infections, rethrombosis, or fasciotomy [10]. Surgical procedures and administration of anesthesia are associated with a complex stress response. The American Society of Anesthesiologists (ASA) grading system offers a simple description of the physical state of a patient and is a component of the overall procedural risk [15]. Despite improvements in pre- and peri-operative management, arterial throm- boembolectomy is characterized by high morbidity and mortality in elderly patients with an ASA score C III [16]. On the other hand, catheter-directed thrombolysis may be effective for treating acute limb ischemia caused by thrombotic or embolic occlusions but it is associated with substantial risk of major hemorrhage and stroke [9, 17, 18]. There are also absolute or relative con- traindications for catheter-directed thrombolysis such us ongoing bleeding, intracranial hemorrhage, compartment syndrome, recent eye surgery, and recent gastrointestinal bleeding. Moreover it cannot be used in patients with severe limb ischemia that require immediate recanaliza- tion due to the longer procedural time [14]. Percutaneous aspiration thrombectomy and percutaneous mechanical thrombectomy are efficient methods for transluminal removal of thrombus but they are associated with high risk for distal embolization (up to 28%), and they also require larger sheaths, which can lead to puncture-site complications (hematoma, dissection) [12].

Reperfusion injury is a common complication after revascularization which can lead to rapid development of compartment syndrome. In this case, surgical fasciotomy is necessary to prevent irreversible neurologic and mus- cular damage [3]. ALLI despite recent advancements in treatment strategies continues to confer significant risks for patients' limb and life, and since currently available surgical or endovascular strategies are not without adverse events and contraindications, there is an obvious necessity for new techniques to be developed.

In this study, we present long-term results in patients with acute arterial occlusions who were treated with direct stenting (stent placement without predilatation of the lesion).

Materials and Methods

Study Design and Patient Selection

This is an observational, retrospective, single-center study aiming to examine efficacy of direct stenting to treat patients presenting with ALLI. Approval was obtained from our institutional review board to conduct this retro- spective study. According to local treatment protocols and in accordance to international guidelines, patients pre- senting with SVS/ISCVS III ALLI (irreversible ischemia) were subjected to primary amputation. Those with SVS/ ISCVS I, IIa, and IIb (viable, marginally, and immediately threatened limbs, respectively) were initially subjected to computed tomography (CT) imaging, and the subsequent management was determined on a consensus between vascular surgeons and interventional radiologists. 24-hour availability of the interventional radiology unit allowed for the alternative of the endovascular treatment to be avail- able even for patients with immediately threatened limbs. Patients were allocated to treatment with direct stenting technique according to the following selection criteria:

1. Compromised patients with ASA score class III or IV who are not ideal candidates for surgery
2. Native artery occlusion (ALLI due to graft thrombosis excluded)
3. Contraindication for administration of thrombolytic agents
4. At least one tibial vessel runoff in the CTA

Patient Data: Clinical Information (Table 1)

Table 1 Clinical data of patients with ALLI

Pt no.	Sex	Age	Risk factors for ALLI	SVS/ISCVS classification	Lesion location	Lesion length (mm)	Duration of symptoms (days)	Contraindications to percutaneous catheter-directed thrombolysis
1	M	63	HT, DM, HL	IIb	(R) SFA	80	2	Severe limb ischemia
2	F	83	HT	IIa	(R) SFA	60	1	Recent eye surgery
3	M	57	HT, HL	IIb	(L) CIA	60	1	Severe limb ischemia
4	M	78	HT, DM, HL, AS	IIb	(L) POPA	100	2	Recent hemorrhagic stroke
5	M	79	DM, HL, AS, AMI	IIb	(R) SFA	120	2	Severe limb ischemia
6	M	55	HL	IIa	(L) EIA	40	6	Severe limb ischemia
7	M	87	HT, SM, CRF	IIb	(R) SFA, (R) POPA	130	3	Severe limb ischemia
8	F	93	DM, HL	IIb	(R) EIA	100	2	Severe limb ischemia
9	M	55	DM, SM	IIb	(R) SFA	40	1	Severe limb ischemia
10	M	52	HT, DM, SM, AMI	IIa	(L) CIA, (L) EIA	100	1	Intracranial trauma 2 months ago
11	F	80	HT, DM, HL, AF	IIa	(L) CIA, (L) EIA	160	1	Diabetic hemorrhagic retinopathy
12	M	79	HT, SM	IIa	(L) CIA	60	4	Severe limb ischemia
13	F	67	DM, AF	IIb	(R) CIA, (R)EIA	80	2	Severe limb ischemia
14	M	66	HL, SM, AF	IIb	(L) EIA, (R) EIA	(L) 80 (R) 100	1	Severe limb ischemia
15	F	61	HT, SM	IIa	(R) SFA (R) POPA	60	1	Recent gastrointestinal bleeding
16	M	90	HT, DM, AF	IIb	(R) POPA	50	2	Severe limb ischemia

M male, *F* female, *HT* hypertension, *DM* diabetes mellitus, *HL* hyperlipidemia, *SM* smoking, *AF* atrial fibrillation, *AMI* acute myocardial infarction, *AS* acute stroke, *CRF* chronic renal failure, *CIA* common iliac artery, *EIA* external iliac artery, *SFA* superficial femoral artery, *POPA* popliteal artery

From January 2010 to September 2015, 120 patients were diagnosed with ALLI at our institution. Among those, 16 patients (11 men and 5 women), aged between 52 and 93 years (median age 72.5 years), underwent direct stenting of acute arterial occlusions. In all patients, the duration of symptoms was less than 2 weeks with a mean duration of 2 days. Cate- gorized in SVS/ISCVS Classification of ALLI, six patients were allocated to class IIa with minimal sensory deficit but no motor deficit and ten patients were allocated to class IIb with sensory deficit and mild to moderate motor deficit. Arterial doppler signal at the level of the malleolus was not detected in the affected limbs of all patients. The affected limbs could be salvageable if immediate revascularization took place.

The main risk factors were hypertension (*n* = 10), hyperlipidemia (*n* = 8), diabetes mellitus (*n* = 9), atrial fibrillation (*n* = 4), smoking (*n* = 6), previous acute myocardial infarction or ischemic stroke (*n* = 4), and previous endovascular or surgical procedure (*n* = 5).

All patients underwent lower extremity CT angiogra- phy (CTA) which revealed occlusions in CIA (n = 5), EIA (n = 7), SFA (n = 6), or POPA (n = 4) taking into consideration that some patients had more than one occlusion. In 12 patients, the cause of ALLI was assumed acute in situ thrombosis in a pre-existing atherosclerotic occlusion while in four patients embolism from the heart. The patients were considered as high risk for surgery due to multiple comorbidities so they were transferred to the interventional radiology suite for endovascular recanal- ization. Catheter-directed thrombolysis was not consid- ered as a treatment option either because it was contraindicated (history of previous intracranial hemor- rhage, recent eye surgery, recent intracranial trauma, diabetic hemorrhagic retinopathy, recent gastrointestinal bleeding) or the severity of limb ischemic symptoms was such that prompted immediate revascularization. Avail- ability of percutaneous mechanical thrombectomy cathe- ters is intermittent in our institute, and there was lack of these devices during treatment of the patients included in our study.

Procedural Details

Percutaneous common femoral arterial access was per- formed under real time U/S guidance. Depending on ipsilateral antegrade or contralateral retrograde approach, 5–6F vascular sheaths of variable lengths were inserted with their tip close to the occluded segment.

Our typical treatment strategy is to initially attempt crossing the occluded segment intraluminally using a 0.035 in. straight or curved hydrophilic guide wire (Terumo, Japan) supported by a standard 5F straight or curved catheter. In all patients, the occlusions were easily tra- versed intraluminally with straight type hydrophilic guide wires, a sign strongly predicting the presence of soft thrombus. Subsequently, self-expanding nitinol stents (Complete, Medtronic), (Luminexx, Bard), (Maris, Med- tronic), (Sinus-SuperFlex, OptiMed), (Zeus SX, Rontis Medical) (Protege Everflex, Covidien) were deployed across the

lesions. The selection of the self-expanding nitinol stent was based on the availability of the desired stent (diameter and length) in our department at that time.

Deployment of a single long stent was preferred over implantation of multiple overlapping stents. Routinely, self-expanding nitinol stents should be 1–2 mm greater than the artery diameter. In our cases, the stent diameter was selected to be similar to the vessel diameter as it was measured before and after the occluded segment to prevent clot prolapse. As far as the stent length, it was about 20 mm longer than the lesion (10 mm proximal and 10 mm distal to the occlusion) to avoid thrombus reloca- tion through both stent ends. Post-dilatation was performed only if there was more than 30% residual stenosis using slightly undersized angioplasty balloons at low pressures to avoid laceration and dislodgement of thrombus which could cause distal embolization. Apart from that the ther- mal memory of self-expanding nitinol stents would allow them to expand at the beneficial size.

The patients received a bolus of 5000 IU of heparin intra-arterially during the procedure. After the endovascu- lar procedure, anticoagulant and antiplatelet therapy was important not only to obtain patency but to prevent recur- rence. Patients with emboli of cardiac origin were placed on long-term anticoagulation with warfarin (INR: 2–3). Patients with non-embolic local arterial thrombosis received dual antiplatelet therapy including clopidogrel (75 mg once daily) and aspirin (100 mg once daily) for 1 month and then aspirin (100 mg once daily) indefinitely.

Endpoints

Primary endpoints of the analysis were efficacy measures of 30-day and long-term survival as well as 30-day and long-term limb salvage rate. Secondary outcomes that were assessed included procedural details like technical success, contrast administration, as well as safety measures like complication rate and distal embolization during

the pro- cedure. Reperfusion injury and need for fasciotomy were recorded. Patients were followed up with clinical examination at 1, 3, 6, and 12 months and color Doppler ultrasound combined with clinical examination on an annual basis. Patency and reintervention rates were also calculated.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). Amputation-free survival and overall survival were evaluated using Kaplan–Meier statistics. Amputation-free survival is a composite metric which incorporates the hard endpoints of mortality and major amputation. Toe and distal foot amputations were considered minor amputations.

Results

Procedural Details: Outcome Measures (Table 2)

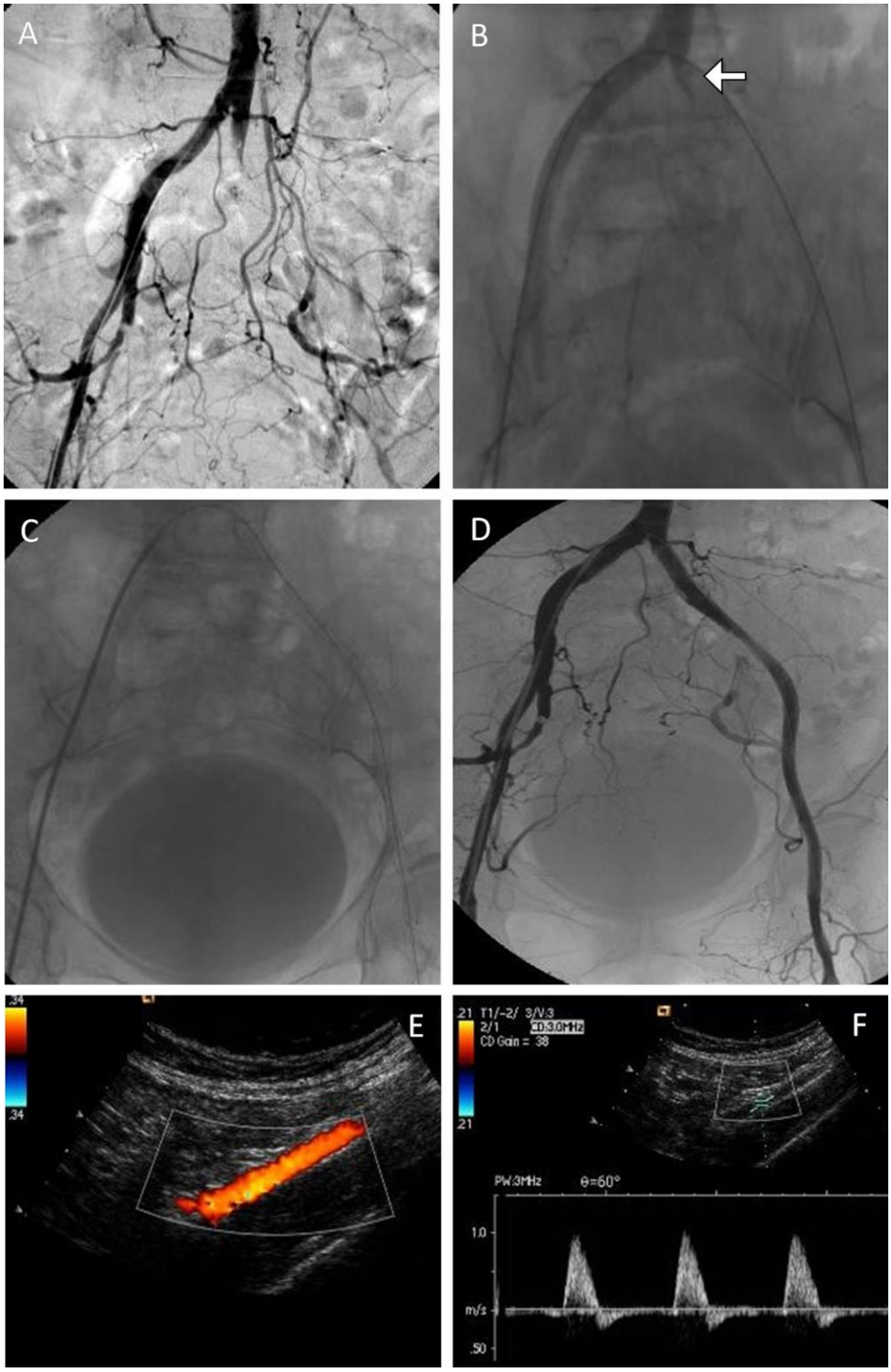
Recanalization was technically successful in all patients. There were no significant residual stenoses in the stented segments and there was neither distal embolization nor acute in-stent thrombosis, as it confirmed with the final angiography (Figs. 1, 2). There were no complications related to femoral arterial catheterizations such as hematomas, pseudoaneurysms, or arteriovenous fistulas. In 15 of 16 patients, there was a significant clinical improvement with immediate relief of symptoms. After the procedure, 14/16 patients restored palpable pedal pulses, while median post-procedural ABI was 0.8 (range 0.2–1.1). During the first week after the procedure, there was one case of in- stent thrombosis followed by above-knee amputation.

Table 2 Procedural details and clinical outcome of patients with ALLI

Technical success	Clinical success	Number of stents used	Type of stent	Post-dilatation	Distal embolization/ reperfusion injury	Duration of follow-up with clinical examination and color duplex U/S (months)	Amputation	Cause of death	In-sten ▯50%
Yes	Yes	2	LUMINEX 7 9 60 mm, LUMINEX 7 9 40 mm	Yes	No	72	Toe amputation 2 months later	Alive	No
Yes	Yes	1	COMPLETE 5 9 80 mm	Yes	No	72	No	Alive	No
Yes	Yes	1	LUMINEX 10 9 80 mm	No	No	72	No	Alive	No
Yes	Yes	1	COMPLETE 6 9 120 mm	Yes	No	1	Toe amputation 1 month later	AMI 12 months later	No
Yes	No	1	COMPLETE 6 9 150 mm	Yes	No	6	Above-knee amputation 1 week later	Alive	In-sten thro 1 we
Yes	Yes	1	LUMINEX 8 9 60 mm	No	No	60	No	Alive	No
Yes	Yes	1	COMPLETE 7 9 150 mm	Yes	No	24	No	Colon cancer 27 months later	No
Yes	Yes	1	MARIS 6 9 120 mm	No	No	24	No	Breast cancer 33 months later	No
Yes	Yes	1	ZEUS SX 6 9 60 mm	No	No	36	No	AIS 40 months later	At pro 2 ye
Yes	Yes	1	MARIS 6 9 120 mm	No	No	60	No	Alive	No
Yes	Yes	1	SINUS-SUPERFLEX 7 9 200 mm	No	No	48	No	Alive	No
Yes	Yes	1	SINUS-SUPERFLEX 9 9 80 mm	Yes	No	48	No	Alive	At pro 3 ye
Yes	Yes	1	ZEUS SX 8 9 100 mm	No	No	36	No	Alive	No
Yes	Yes	2	PROTEGE EVERFLEX 7 9 100 mm, 7 9 120 mm	Yes	No	24	No	Alive	No
Yes	Yes	1	PROTEGE EVERFLEX 5 9 80 mm	Yes	No	12	No	Alive	No
Yes	Yes	1	PROTEGE EVERFLEX 6 9 60 mm	Yes	No	6	No	Alive	No

AIS acute ischemic stroke, *AMI* acute myocardial infarction

Fig. 1 A 80-year-old patient with atrial fibrillation. A DSA showed total occlusion of left CIA and left EIA. B Through percutaneous crossover approach from the right common femoral artery, the acute occlusion was traversed with a hydrophilic guide wire. Note the left CIA filling defect in the proximal end of the occlusion (arrow), typical for acute thrombus. C A self-expanding 7 9 200 mm nitinol stent was deployed across the lesion and D flow restoration was immediately achieved without distal embolization or other complications. E, F 4 years later the patient was asymptomatic. On color Duplex follow-up, the stented segment and distal runoff arteries remained patent with no significant restenosis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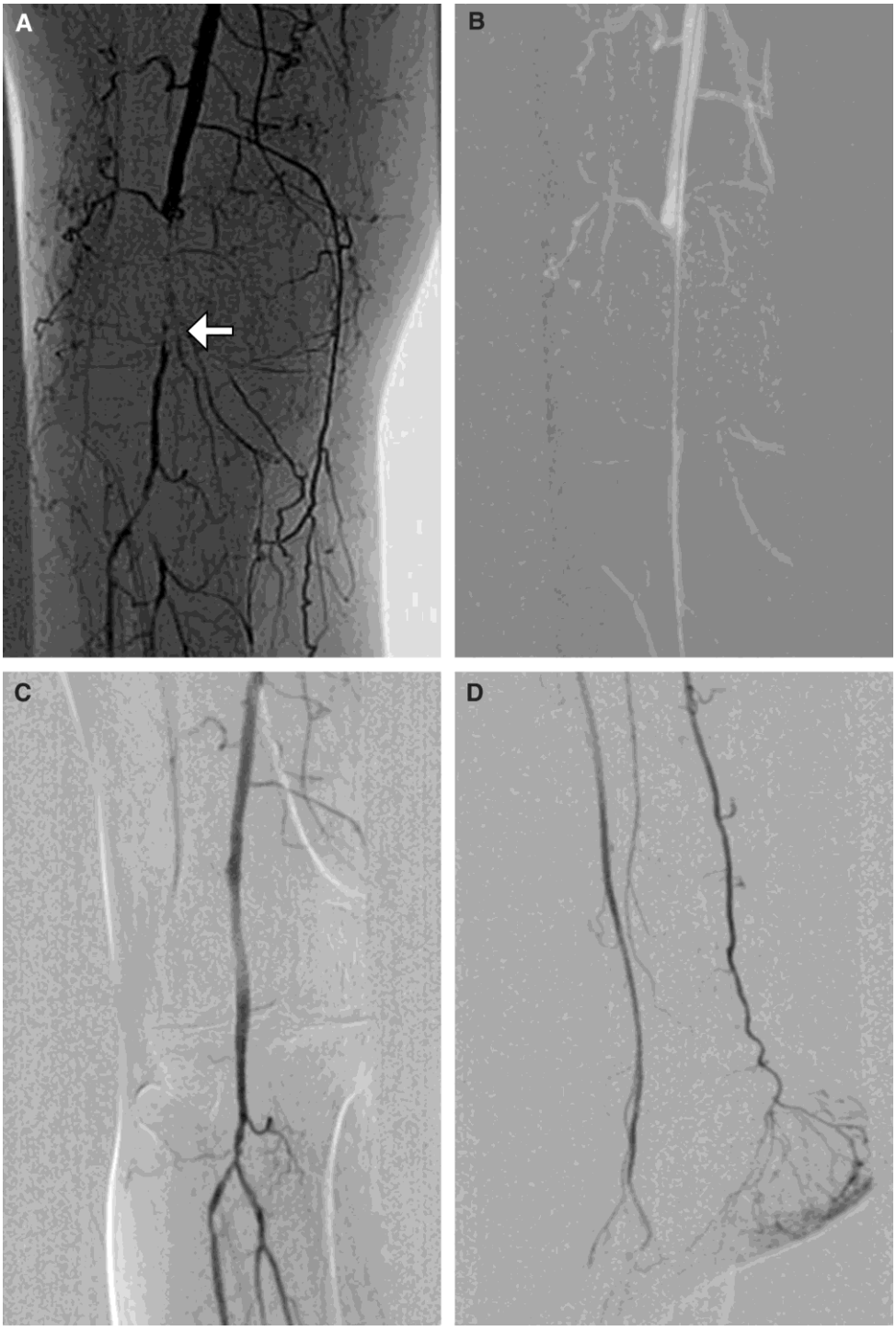
The patients were followed up with clinical examination and color Duplex ultrasonography for a mean duration period of 37.6 months (SD 24.9 months, range 1–72). During follow-up, four patients died due to non-procedure-related causes (colon cancer, breast cancer, myocardial infarction, ischemic stroke) and there were two minor (toe) amputations and one major (above-knee) amputation. The amputations took place during the first year after the procedure. The 1-, 3- and 6-year survival rates, estimated by Kaplan– Meier analysis, were 93.3% [95% confidence interval (CI) 61.2–99%], 77.8% (95% CI 45.5–92.3%), and 69.1% (95% CI 36.7–87.3%), respectively, and the 1-, 3- and 6-year Amputation-free survival rates were 87% (95% CI 57.3–96.6%), 71.2% (95% CI 39.8–88.2%), and 62.3% (95% CI 31–82.6%), respectively (Fig. 3). The primary patency rate (defined as exempt from in-stent-restenosis greater than 50%) was 93.7% (95% CI 63.2–99.1%) at 1 year, 85.9% (95% CI 54–96.3%) at 2 years, and 75.2% (95% CI 39.4–91.6%) at 3 to 6 years (Fig. 4). No reper- fusion injury was observed in this series and fasciotomy was not necessary in any of the patients treated.

Fig. 2 A 91-year-old patient with right acute lower limb ischemia. A DSA showed a thrombotic occlusion of the right popliteal artery with a small intraluminal filling defect in the distal end of the occlusion (arrow) consistent with the presence of fresh thrombus. B The occlusion was intraluminally traversed with a hydrophilic guide wire. C Following the implantation of a 6 9 60 mm self-expanding nitinol stent, DSA demonstrated significant flow restoration. D Conclusion DSA showed no evidence of distal embolization in the distal runoff arteries.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Discussion

Acute limb ischemia is a sudden decrease in limb perfusion that threatens the viability of the extremity and requires immediate revascularization.

Stenting has been used successfully in acute myocardial infarction after failed thrombolysis [19] or after unsuccessful emergency angioplasty [20] but is also an effective primary revascularization strategy with many advantages compared with PTCA [21]. Primary intracranial stenting is also a safe and feasible approach for patients with acute ischemic stroke [22, 23]. Moreover, primary or direct stenting is an acceptable revascularization treatment for peripheral artery disease [1]. It is effective both for iliac artery occlusive disease [24] and femoropopliteal disease [25]. Direct stenting is not considered as a standard treat- ment option for ALLI due to a risk of distal embolization, which worsens the ischemia. So far there are only a few reports of patients with ALLI treated with stenting. Yilmaz et al. treated six patients with embolic occlusions in the common or external iliac arteries with primary stenting without complications [26]. Berczi et al. reported seven patients with acute thrombotic occlusions in the iliac arteries, who underwent stent implantation with no significant embolic complications [27]. Raja et al. reviewed 4 patients with acute thrombotic or embolic occlusions in iliac or femoropopliteal arteries who were treated with stenting [28]. Finally Kim et al. treated fifteen patients with ALLI with stent implantation with significant technical and clinical success [29].

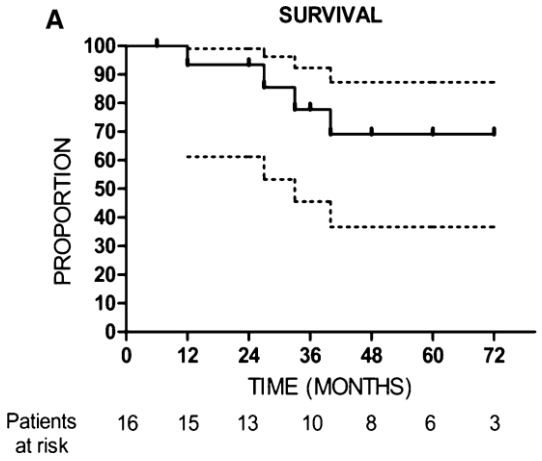
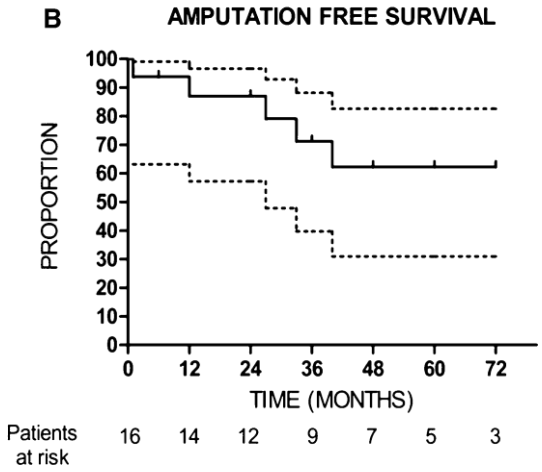


Fig. 3 The survival curves (±95% confidence interval) were calcu- lated by Kaplan–Meier method. The *x*-axis shows months of follow- up, the *y*-axis shows proportion of patients remaining alive (A) or alive without major amputation (B). The number of patients at risk is indicated for each time point during follow-up



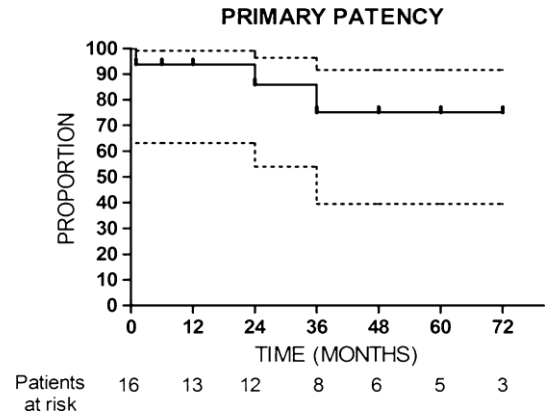


Fig. 4 Kaplan–Meier curve of primary patency (±95% confidence interval) after stent placement. The number of patients at risk for each follow-up period is also indicated

Our study includes the largest number of patients with ALLI, treated with primary or direct stenting (*n* = 16) and the longest follow-up (mean duration of about 3 years), which confirms a sustainable clinical improvement and low risk for amputation. In our study, we applied direct stenting as a primary endovascular treatment due to unavailability of percutaneous mechanical thrombectomy catheters at the time of cases presentation, while catheter-directed throm- bolysis was either contraindicated or was considered too time consuming for immediate limb revascularization. Our findings indicate that direct stenting is an attractive therapeutic alternative for the management of patients with ALLI whenever feasible. The 100% technical success rate recorded in our study cohort compares favorably with the results of other reports employing the traditional and widely accepted techniques of catheter-directed thrombolysis and percutaneous mechanical thrombectomy. Fur- thermore, we neither encountered puncture-site complications nor distal embolization which confirms the safety of this technique in patients with ALLI. From our clinical experience, immediate recanalization of acute arterial occlusions with direct stenting did not induce compartment syndrome or systemic inflammatory response triggered by reperfusion injury in any patients at least to an extent that needed any further concomitant treatment. We used only self-expanding nitinol stents to avoid laceration and dislodgement of thrombus and reduce the traumatic injury of the vessel. Drug-eluting stents (DES) improve patency rates and reduce the risk of reintervention com- pared with PTA or bare-metal stents (BMS) in atherosclerotic disease of femoral, popliteal [30], and infrapopliteal arteries [31]. However, there are no reported cases of the use of DES in ALLI. Stents in the femoropopliteal system and especially if the lesions expanded in the inguinal ligament or knee joint have historically been associated with increased rate of stent fracture and restenosis. Modern self-expanding nitinol stents with their resistance to external deformation and their thermal memory properties are sometimes indicated for placement in areas of flexion (close to the inguinal ligament, in the adductor canal and at the knee

joint) [32]. Multiple studies have reported the use of flexible self-expanding nitinol stents in the popliteal artery and lesions which were extended into the below-knee segment with good patency rates [33]. In our study, we avoided stent placement when the lesion crossing joints and there was only one patient (Fig. 2) who underwent direct stenting of popliteal artery occlusion crossing the knee joint. This patient was 90-year- old, presenting multiple comorbidities and was partially immobilized for 2 years. Therefore, he was a poor surgical candidate presenting also contraindication for catheter-directed thrombolysis. In this instance, direct stenting seemed an appealing therapeutic option even if the stent would be crossing the knee joint. Despite the fact that the lesions observed in this series were relatively long, tech- nical success was achieved in all patients. Other authors who performed direct stenting for ALLI encountered similar long arterial occlusions (up to 150 mm) [26–29]. All stents deployed in the studied patients were commercially available self-expanding nitinol ones with different strut configuration and it would be interesting to analyze in larger cohort studies the potential influence of strut design to overall nitinol stent performance in the ALLI setting.

In conclusion, direct stenting appears to be a safe, effective, and durable treatment for patients with ALLI who require immediate recanalization and they have contraindications for catheter-directed thrombolysis or surgical revascularization.

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Section 5

Relevant Research 2:

Incidence and Endovascular Treatment of Isolated Atherosclerotic Popliteal Artery Disease: Outcomes from the IPAD Multicenter Study

Introduction

Minimal invasive, percutaneous, endovascular treatment is continuously gaining ground as a first-line treatment of intermittent claudication (IC) or critical limb ischemia (CLI). This is mainly due to the increasing experience and the improvement of endovascular devices, both resulting in constantly increasing technical success and lower complication rates, even in complex peripheral arterial disease (PAD) cases [1, 2]. One of the most challenging anatomical locations for endovascular treatment of atherosclerotic disease has always been the popliteal artery [3]. The specific anatomical location and unique biomechanical attributes of the popliteal artery result in low mid-term patency rates following plain balloon angioplasty, while stenting has been traditionally reserved for bail-out cases due to the increased risk of stent deformation or fracture which has been related to decreased patency [4]. Moreover, a recent multicenter, randomized controlled trial (RCT), investigating stenting versus plain balloon angioplasty for popliteal artery treatment demonstrated comparable 2-year patency rates following either provisional or primary stenting [5].

Although endovascular treatment options to improve immediate technical success and long-term patency of femoropopliteal atherosclerotic arterial disease has been widely investigated in several, large-scale, multicenter RCTs, data regarding the

performance of angioplasty and bail-out stenting in isolated atherosclerotic popliteal artery disease (IPAD) remain limited to one multicenter RCT and few single-center, retrospective analyses, while long-term data, beyond 2 years, do not exist [5–10].

The aim of this multicenter study was to investigate the incidence and long-term outcomes of angioplasty and bail- out stenting for the treatment of IPAD performed in the Interventional Radiology Departments of three large, ter- tiary University Hospitals.

Materials and Methods

This retrospective, multicenter, single-arm study included all patients undergoing endovascular treatment of IPAD between January 2010 and December 2016 because of intermittent claudication or critical limb ischemia (CLI), in three tertiary Hospitals. In total, 4717 peripheral arterial disease procedures were performed within the study period. The patients' medical and imaging records were scrutinized. Inclusion criteria were: age C 18 years old, Rutherford–Becker classification between 2 and 5, de novo C 50% angiographic stenosis or occlusion in the PA according to visual estimation and treatment with plain balloon angioplasty and/or bare metal stenting. The PA was radiographically divided into three segments as follows: P1 (between the arterial intersection with the femoral bone and the upper edge of the patella), P2 (between the upper limit of the patella and the superior surface of the tibial condyle) and P3 (between the superior surface of the tibial condyle and the infrapopliteal arterial bifurcation of the anterior tibial artery and the tibioperoneal trunk). Exclusion criteria were: lesions requiring intervention (endovascular or surgical) involving the proximal inflow (aorta, iliac arteries, common femoral artery, SFA) or the arterial outflow (infrapopliteal arteries), and standard angioplasty contraindications (pregnancy, uncorrectable coagulopathy, impaired renal status and history of severe, life-threatening allergy to contrast).

The decision to proceed with endovascular rather than surgical treatment was discussed at the multidisciplinary team meeting between vascular surgeons and interventional radiologists and was case-sensitive. In general, endovascular revascularization was decided for patients at high-surgical risk or those with stenosis or short occlu- sions. Procedures were performed using standard endovascular techniques [5, 8]. In brief, all patients were prescribed antiplatelet therapy (monotherapy with aspirin 100 mg or clopidogrel 75 mg once daily or dual therapy with aspirin 100 mg and clopidogrel 75 mg once daily according to the physicians' preference) at least 5 days prior to the procedure. Following the placement of an arterial sheath, a bolus dose of 5000 IU of heparin was administered. Intraluminal or subintimal lesion crossing was performed, using standard guide wires and catheters. Balloon angioplasty was the initial treatment of choice, and bail-out stenting was used in cases of suboptimal angioplasty result ([30% remaining stenosis by visual estimation and flow-limiting type C dissection). Hemosta- sis was achieved by either manual compression or arterial closure devices. After the procedure, antiplatelet therapy regiment and duration was administrated on a case basis and according to the physicians' preference. In general, dual antiplatelet therapy with clopidogrel 75 mg and aspirin 100 mg once daily was administrated for at least one month and up to 6 months, following the procedure and single antiplatelet therapy with either clopidogrel 75 mg or aspirin 100 mg once daily was then continued for life. Procedural details are reported in Table 1.

Definitions Endpoints and Follow-up

The study's primary outcome measures were: (1) IPAD incidence defined as the proportion of patients receiving endovascular treatment for IPAD within the population of patients who received endovascular treatment for PAD during the 7-year study period. (2) Binary restenosis defined as C 50% restenosis of the target lesion according

Table 1 Patient demographics

Variable	*N* (%)
Patients	46
Limbs	46
Male	32 (82.6)
Age; mean ± SD (range)	73 ± 12 (48–90)
Cardiac disease	21 (45.6)
Diabetes mellitus	35 (76.1)
Renal disease	11 (23.9)
Hyperlipidemia	31 (67.4)
Smoking habit	13 (28.2)
Hypertension	35 (76.1)
Stroke/TIA	8 (17.4)
Rutherford–Becker classification	
3	16 (34.8)
4	11 (23.9)
5	18 (39.1)
6	1 (2.2)

to duplex ultrasound (DUS; peak systolic velocity ratio [2.4) or digital subtracted angiography (DSA; per- formed in cases of re-intervention) and (3) freedom from clinically driven (symptoms relapse) target lesion revas- cularization (TLR) due to angiographically verified (intra-procedural) target lesion restenosis. Secondary outcome measures were technical success defined as residual target lesion stenosis of \ 30% (by visual estimation) without type C (flow limiting) target vessel dissection at comple- tion DSA following balloon angioplasty or stenting, limb salvage (i.e., amputation above the level of the ankle), and complications defined as major or minor according to international guidelines [11], as well as the identification of independent predictors of outcomes. Severe calcifications of the lesion were defined as radiopacities on both sides of the arterial wall and extending [1 cm of

length at plain fluoroscopy. Mild calcifications were defined as calcifica- tions noted without fulfilling all previous criteria.

Follow-up visits were scheduled at 6 and 12 months and yearly thereafter (unless a non-scheduled visit was required due to relapse) and included clinical examination, Rutherford–Becker classification of the disease and target lesion evaluation by DUS.

Statistical Analysis

Discrete variables are reported as counts and percentages, while continuous variables as medians and interquartile ranges (i.e., between the 25th and 75th percentiles) in parentheses or as mean ± standard error (SE) if they pas- sed the normality test as stated below. The Kaplan–Meier analysis method was employed for calculation of the cumulative proportion outcomes of restenosis, TLR-free, survival and limb salvage rates. Exploratory univariate subgroup analysis for primary and secondary outcome measures was performed using the following dependent variables: baseline symptoms (critical limb ischemia or intermittent claudication), diabetes mellitus, increased serum creatinine level ([1.5 mg/dL), nicotine use (up to the preceding 12 months), cardiac disease (coronary disease, cardiac insufficiency, severe arrhythmia), hyperlipidemia (controlled with diet or drugs), initial lesion grade (stenosis or occlusion), TASC II lesion classification, runoff vessels (1–3), severe calcifications of the lesion defined as radiopacities on both sides of the arterial wall and extending [1 cm of length at plain fluoroscopy, popliteal segment (P1, P2, P3), subintimal or intraluminal lesion crossing and treatment modality (plain balloon angioplasty or stenting). Covariates with a p value \ 0.15 according to an exploratory univariate analysis were included in the Cox multivariable stepwise regression analysis that was employed in order to identify independent risk factors affecting the study's outcome measures. Finally, the dependent variables assessed by the Cox multivariate stepwise regression analysis were

stent deployment, cardiac disease, diabetes mellitus and baseline lesion grade. The results were expressed as hazard ratios with 95% confidence intervals (CIs) and the associated level of statistical significance, while the adjusted Cox curve plots of the identified covariate are presented only in cases of significant outcomes. Statistical analysis was performed with the SPSS statistical software package (version 21.0; IBM, USA), with a threshold for statistical significance at a p value of 0.05.

Results

The incidence of IPAD was 0.98% (46/4717 peripheral arterial disease procedures). In total, 46 patients (38 male; 82.6%), with a mean age of 73 ± 12 years (range 48–90 years), underwent 32 plain balloon (69.5%) or 14 bail-out nitinol bare stent deployment (30.5%) procedures in 46 limbs. Stents used in this study were the S.M.A.R.T.® CONTROL® Self-Expanding Nitinol Stent (Cordis, Switzerland), the EVERFLEXTM Self-Expanding Periph- eral Stent and the Complete® SE Vascular Stent System (Medtronic, USA) and the ZeusTM SX Nitinol Self-Expanding Stent System (Rontis Medical, Switzerland). Stent diameters were either 5 or 7 mm. Most patients suffered from CLI (30/46 cases; 65.2%), while 76.5% (35/46 cases) had diabetes, 32.9% (11/46 cases) were on dialysis and 28.2% (13/46) were active or recent smokers. Mean lesion length was 52.5 ± 32.0 mm (range 20–120 mm) with 45.6% of the lesions being occlusions (21/46 cases). In 15/46 cases (32.6%) the P2 segment and in 13/46 cases (28.3%) the infrapopliteal P3 segment were treated.

Technical success was 100% (46/46 cases). The subin- timal technique was used in only 3/46 cases (6.5%). Severe calcifications were noted in 26.1% (12/46 cases) and mild calcifications in 15/46 cases (32.6%). Major complications did not occur. Minor complications included 6 small \ 5 cm puncture-related groin hematomas (6/46; 13.0%). Patient demographics and procedural details are analytically reported in Table

1. Mean time follow-up was 32.6 ± 25.6 months (range 4–94 months). According to Kaplan–Meier analysis, restenosis was 15.8, 40.9, 45.8% (numbers at risk: 27, 12, 9) and TLR-free interval was 90.5, 79.0, 74.1% (numbers at risk: 32, 20, 10), at 1, 2 and 3 years follow-up, respectively (Fig. 1). Patient survival rate was 97.5, 91.3 and 73.6% (numbers at risk: 40, 21, 9), and limb salvage was 95.4, 95.4 and 88.1% (numbers at risk: 39, 24, 12), at 1, 2 and 5-year follow-up; respectively (Fig. 1). The major amputation rate in the subgroup of patients suffering from CLI was 10.0% (3/29 limbs), while no major amputations occurred in the clau- dication subgroup. In total, 2/46 patients (4.3%) underwent bypass surgery due to lesion re-occlusion and symptoms relapse. The median (interquartile range) Rutherford class decreased from 4 (3–5) at baseline to 2 (1–2) at 1 month, 2 (1–3) at 12 months and 2 (2–3) at 5 years, respectively. A Rutherford classification improvement by at least 1-class compared to baseline was noted in 93.5% of the patients (43/46 cases) at one month, in 89.1% (41/46 cases) at 12 months and in 78.2% (36/46) at 5 years (Table 2).

Subgroup analysis of bail-out stenting versus plain bal- loon angioplasty demonstrated similar TLR-free (92.3 vs. 89.0%; p = 0.13, respectively at 1-year follow-up) and restenosis rates (84.6 vs. 80.0%; p = 0.17, at 1-year follow- up). According to Cox multivariable analysis, the only independent predictor of increased restenosis was baseline occlusion of the treated lesion (HR 5.3; 95% CI 0.21–0.66, p = 0.02) (Fig. 2).

Discussion

The importance of the herein presented results is that the incidence of IPAD was defined in a real-life multicenter clinical scenario, while the treatment strategy of plain balloon angioplasty with bail-out bare metal stenting resulted in acceptable outcomes up to 5-year follow-up. Specifically, the study involved three major tertiary, high volume, vascular centers, performing over 700 lower limb, chronic PAD, endovascular procedures per year. IPAD accounts for approximately

1% of lower limb endovascular revascularizations. Long-term restenosis and revascular- ization rates were low. Specifically, restenosis was nearly 50% at 3-year follow-up and consequently only 25% of the patients underwent re-intervention due to clinical relapse, during the same time period. These results are comparable to previously reported restenosis rates following IPAD treatment [4, 5]. Specifically, a recent multicenter RCT comparing stenting versus plain balloon angioplasty for IPAD, conducted by Rastan et al., reported similar 2-year restenosis rates of 35.8% in the stent group but higher for the PTA group (68.8%). Nevertheless, TLR rates were around 30% for both groups [5]. Interestingly, the reported restenosis rates following plain balloon angioplasty or stenting of the femoropopliteal arteries are significantly higher around 50–60% at 1 year [12–14]. One could speculate that IPAD cases demonstrate lower restenosis due to the short lesion length and the disease-free arterial inflow and outflow [15]. Lesion length and severe calcifi- cations are two well-known independent predictors of decreased patency [16, 17]. In this study, almost half of the lesions were occlusions, and mean lesion length was short (approx 5 cm), while severe calcifications were noted only in 25% of the lesions. Interestingly, according to the multivariable analysis, baseline lesion occlusion was the only independent predictor of increased restenosis. Reduced patency following endovascular treatment of occlusions has been previously reported in the literature [18]. Nonetheless, other factors that have been usually correlated with worst outcomes such as diabetes, severe calcifications and lesion length were not verified in this

analysis [4, 15, 17]. This could be attributed to the small number of patients which certainly limited the validity of statistical analysis for these factors.

As for SFA lesions, primary stent deployment in the popliteal artery remains controversial [5, 17, 19]. Accord- ing to subgroup analysis performed in this study, bail-out stenting achieved similar restenosis and re-intervention rates, while multivariable analysis indicated that stenting did not significantly improve outcomes. Stenting rate in this

study (30.5%) was similar with previously published data investigating popliteal disease. Specifically, Chang et al. have reported a 35.6% stenting rate for popliteal lesions (18/52 cases) [4]. It could be discussed that stenting rate is high. Indeed, as this was a retrospective analysis without uniform predetermined criteria for bail-out stent- ing, cases of inappropriate bail-out stenting cannot be excluded. On the other hand, 45% of the lesions treated were chronic total occlusions and 26% were severely cal- cified, and thus a 30% stenting rate is probably justified. Bail-out nitinol stent deployment resulted in satisfactory outcomes aligned with previously reported data for IPAD endovascular treatment [5]. Following these results, the authors will continue to use nitinol stents as a bail-out option for IPAD.

The use of novel interwoven stents, heparin-bonded stents or drug-eluting stents could further increase the patency of endovascular IPAD treatment [20]. On the other hand, in an area of high flexion such as the popliteal artery, drug-coated balloons, atherectomy devices and their combination should be further investigated as these techniques could offer superior technical success rates with less dissection and recoil combined with superior patency rates without the use of metallic implants [21–23]. According to the authors' experience, a significant draw- back of popliteal stenting is the increased difficulty of future endovascular revascularization in case of stent occlusion and a future surgical bypass inhibition. The 5-year limb salvage rate was 88% and overall, three major amputations occurred (6.5%) all in CLI patients with Rutherford–Becker class 5 disease.

The major amputation rate in the CLI subgroup was 10.0%, while no major amputations were noted in the claudication subgroup throughout the follow-up period, a fact that further supports the long-term safety of the method.

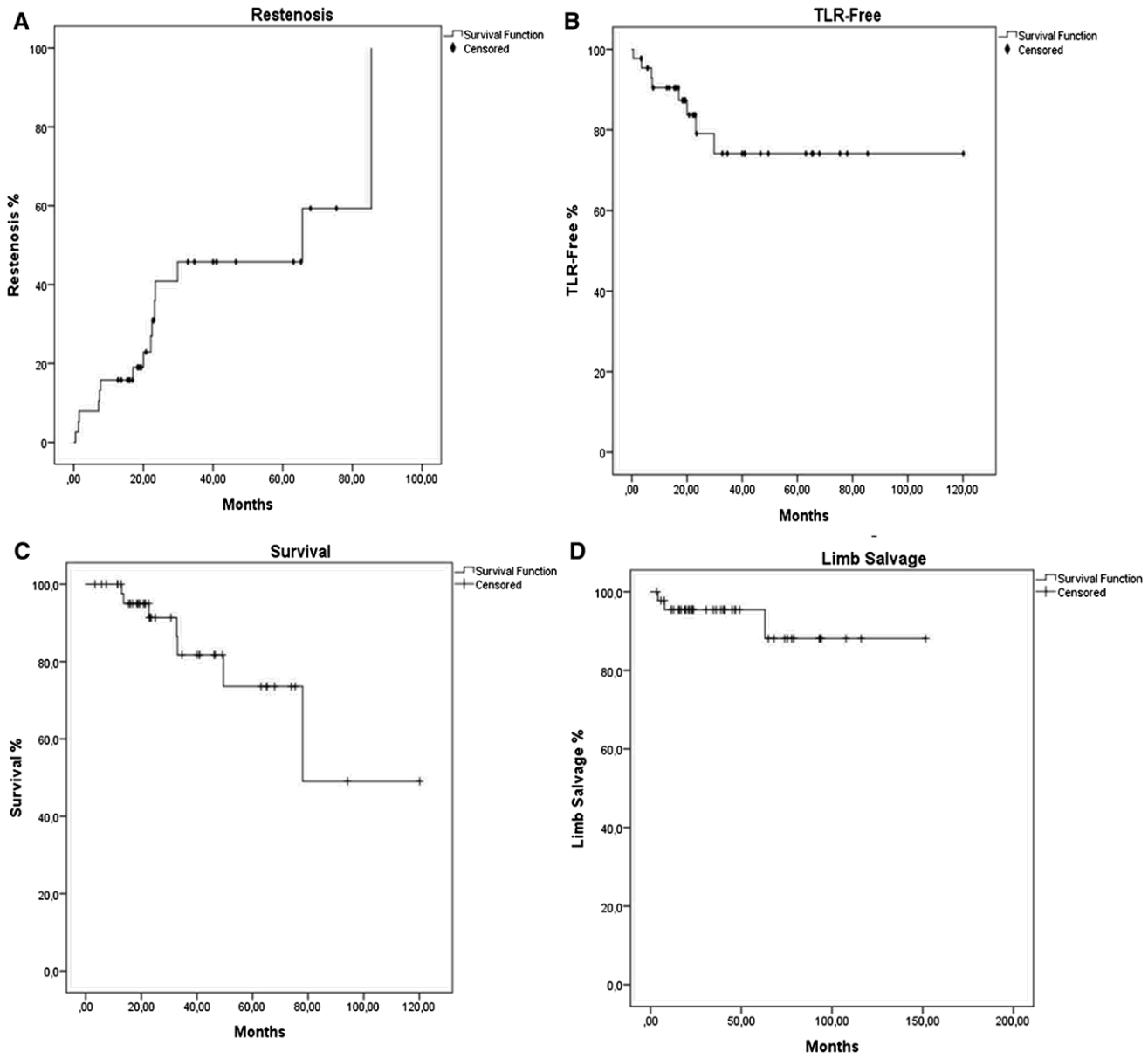

Fig. 1 Kaplan–Meier plots of A restenosis, B target lesion revascularization-free, C patient survival and D limb salvage rates

Table 2 Procedural details

Variable	*N* (%)
Lesions	46
Mean lesion length (mm)	52.5 ± 32.0
Popliteal segment treated	
P1	8 (17.4%)
P2	15 (32.6%)
P3	5 (10.8%)
P1–P2	10 (21.7%)
P2–P3	6 (13.0%)
P1–P2–P3	2 (4.3%)
Occlusions	21 (45.6%)
Calcifications	
None	19 (41.3%)
Mild	15 (32.6%)
Severe	12 (26.1)
Number of runoff vessels*	2 (2–3) Sheath size
4Fr	5 (10.8%)
6Fr	40 (86.9%)
7Fr	1 (2.3%)
Antegrade access	38 (82.6%)
Antiplatelet therapy	
Monotherapy	21 (45.6%)
Dual therapy	25 (54.4%)
Treatment type	
Balloon angioplasty	32 (69.5%)
Stent	14 (30.5%)

Continuous data are presented as mean ± SE; categorical data are given as counts and percentages (parentheses)
*Median value and interquartile range (IQR) in the parentheses

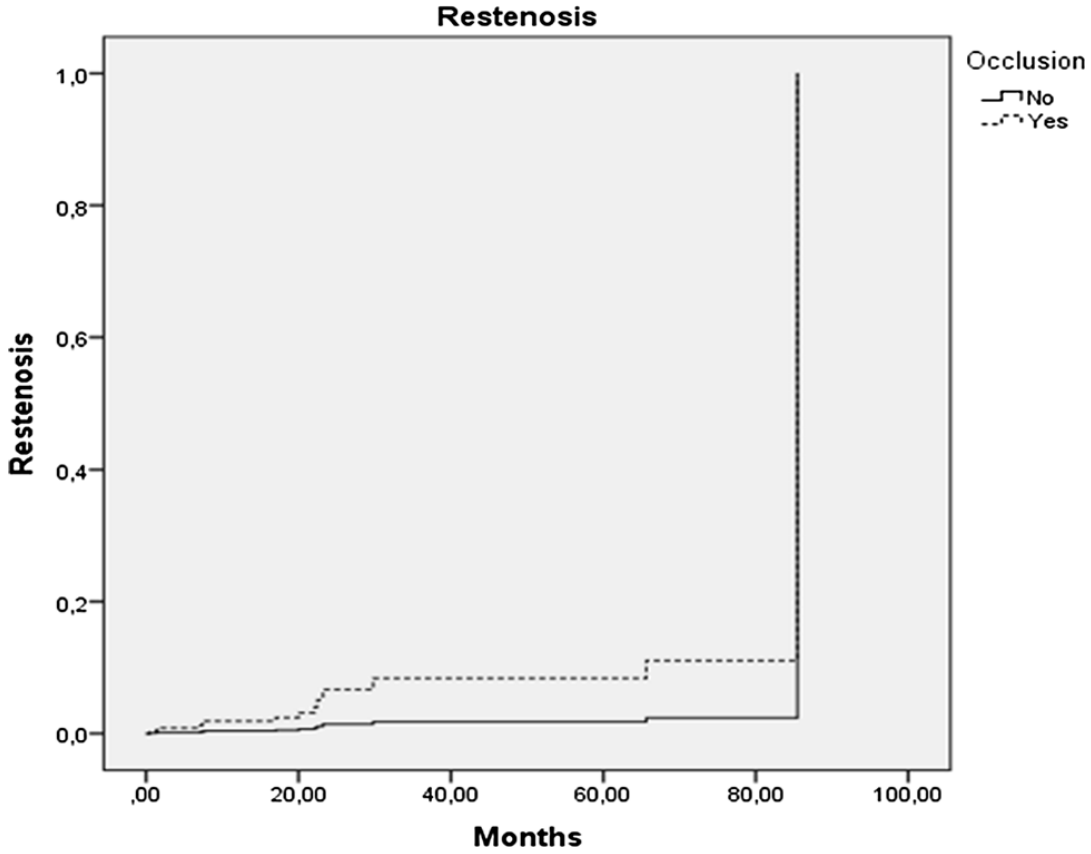

Fig. 2 Cox multivariable analysis plot of target lesion restenosis rate stratified according to baseline lesion grade (stenosis or occlusion)

Limitations of this study include: (1) the retrospective nature of investigation which might have influenced data quality as some parameters such as ABI values and wound healing data could not be retrieved in the majority of the patients and therefore were not reported, while a small number of cases might have been missed (2) the single-arm design, which does not allow treatment comparisons and (3) the relatively small number of patients which certainly reduces the credibility of both univariate subgroup and multivariable analysis in detecting factors associated with outcomes. Nonetheless, Kaplan–Meier analysis should be considered statistically sound, at 3 years for restenosis and TLR-free interval and at 5 years for amputation and sur- vival as the SE remained below 10% at these specific time-points. (4) The multicenter retrospective design did not allow for a uniform protocol for the detection of restenosis and as a result two

different imaging modalities (DUS or DSA) have been implemented. (5) The statistical value of outcomes at 3 years and beyond was significantly decreased for restenosis and TLR and therefore data are not presented, while the 5-year survival outcome is restricted by the fact that numbers at risk decreased to 9.

In conclusion, according to the results of this multi-center study, IPAD is an uncommon subgroup of PAD. The treatment strategy of plain balloon angioplasty and bail-out stenting resulted in acceptable long-term clinical outcomes. Treatment of occlusions was correlated with increased restenosis rate. In light of the fact that newer and more expensive endovascular technologies have been emerged for the management of popliteal disease, these data cer- tainly merit further investigation with larger, prospective, randomized trials in order to establish the appropriate endovascular treatment protocol for IPAD.

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PART IV

Final Remarks

Section 1

Primary Protocol

Feasibility of ischemic leg ulcer healing using percutaneous techniques: a real-life study

Our data support the technical and clinical success of PTA in the management of ischemic foot ulcers with high rates of healing and limb salvage. PTA was technically successful and feasible in almost all patients with only a minority of cases unsuitable for percutaneous techniques due to extensive and complex distribution of atherosclerotic lesions.

Another important aspect of our study is that most of the patients' lesions were classified as TASC II Type C and D, with 98% and 95% technical success respectively, indicating that endovascular procedures can be performed in patients to whom surgical intervention was previously recommended.

In conclusion, endovascular intervention as first-line treatment in subjects with arterial insufficiency and ischemic foot ulcers is feasible in the vast majority of patients, and has a very high technical success rate. Percutaneous revascularization results in a high overall incidence of wound healing and limb salvage, accompanied by very low morbidity and

mortality rates. Factors that affect clinical success, potentially affecting optimal treatment strategy are the extent of tissue destruction at presentation, along with patient comorbidities.

Additional Protocol 1:

Vibrational angioplasty in recanalization of chronic femoropopliteal arterial occlusions: Single center experience

Chronic Total Occlusions (CTOs) are commonly found in patients with PAOD, occurring in up to 40% of symptomatic patients.

Approximately one-third of femoropopliteal PTAs are currently performed in the setting of CTOs with an average of 20% procedural failure rate using traditional guidewire and balloon technology.

The causes of failure are the complexity of these lesions and the difficulty of crossing the site of occlusion with conventional guidewires or the inability to reenter the distal true lumen from a subintimal path. In comparison with simple stenoses and acute occlusions, recanalization of CTOs is associated with lower technical success rates, higher complication rates – such as distal embolization and perforation – longer procedural times as well as elevated radiation dose levels for patients and staff.

Vibrational angioplasty is a low-energy technique that facilitates intraluminal navigation of guidewires through resistant lesions, avoiding

the damage of the collateral vessels and causing less vascular trauma. Initially it was applied successfully in recanalization of chronic coronary total occlusions.

Vibrational angioplasty was performed by a hand–held motorized device, designed to impart vibrational motion to a guidewire in order to facilitate crossing of the occlusion (Fig. 1). The device accommodates guidewires of up to 0.018 in. in diameter and gen- erates a combined reciprocal and lateral movement at the tip of the wire with a range of frequencies from 16 to 100 Hz. The duration of each activation ranged from 1 to 2 min.

In conclusion, vibrational angioplasty is a safe, effective and durable endovascular technique for the treatment of chronic femoropopliteal total occlusions in patients that would be difficult to recanalize using conventional techniques.

Additional Protocol 2:

Effectiveness of Platelet-Rich Plasma to Enhance Healing of Diabetic Foot Ulcers in Patients With Concomitant Peripheral Arterial Disease and Critical Limb Ischemia

Diabetic foot ulceration (DFU) is an unavoidable event dur-ng the clinical course of many patients, up to 25% of whom will suffer from a foot ulcer during their lifetime. Approximately 20% of these ulcers ultimately require amputation and 85% of all diabetic lower limb amputations are preceded by an ulcer.2 It is worth noting that these patients are 15 to 30 times more likely to undergo an amputation than those without diabetes.

However, these therapeutic measures can succeed only in the presence of adequate arterial perfusion. Subsequently, aggressive attempts for revascularization are indicated as one of the first and most important measures to enhance ulcer healing and maximize possibilities for limb salvage.

In the current study, we attempted to examine the efficacy of autologous platelet-rich plasma (PRP) for the treat- ment of DFU in patients with concomitant PAD. Subjects in the most severe spectrum of arterial

disease, meaning those with CLI, were also included. In this regard, our research aims

Overall, 72 patients were eligible to be included in the cur- rent analysis

In conclusion, PRP is an effective adjunct to enhance would healing and increase limb salvage in diabetic patients with concomitant PAD. Limb loss is significantly higher in diabetic patients presenting with CLI compared with those without and therefore revascularization should be attempted in the former group. Nevertheless, GFs may be used even in patients with CLI to assist treatment of foot ulceration.

Section 2

Relevant Research 1

Direct Stenting in Patients with Acute Lower Limb Arterial Occlusions: Immediate and Long-Term Results

In this study, we present long-term results in patients with acute arterial occlusions who were treated with direct stenting (stent placement without predilatation of the lesion).

From January 2010 to September 2015, 120 patients were diagnosed with ALLI at our institution. Among those, 16 patients (11 men and 5 women), aged between 52 and 93 years (median age 72.5 years), underwent direct stenting of acute arterial occlusions

Recanalization was technically successful in all patients.

In 15 of 16 patients, there was a significant clinical improvement with immediate relief of symptoms.

In conclusion, direct stenting appears to be a safe, effective, and durable treatment for patients with ALLI who require immediate recanalization and they have contraindications for catheter-directed thrombolysis or surgical revascularization.

Relevant Research 2

Incidence and Endovascular Treatment of Isolated Atherosclerotic Popliteal Artery Disease: Outcomes from the IPAD Multicenter Study

One of the most challenging anatomical locations for endovascular treatment of atherosclerotic disease has always been the popliteal artery

The aim of this multicenter study was to investigate the incidence and long-term outcomes of angioplasty and bail-out stenting for the treatment of IPAD performed in the Interventional Radiology Departments of three large, tertiary University Hospitals.

In conclusion, according to the results of this multi- center study, IPAD is an uncommon subgroup of PAD. The treatment strategy of plain balloon angioplasty and bail-out stenting resulted in acceptable long-term clinical outcomes. Treatment of occlusions was correlated with increased restenosis rate

Relevant Research 3

Occupational exposure during endovascular aneurysm repair (EVAR) and aortoiliac percutaneous transluminal angioplasty (PTA) procedures

The use of fluoroscopy in PTA and EVAR procedures leads to considerable radiation doses for interventionalists. Only a few studies have evaluated the radiation exposure of primary operator's radiosensitive organs such as thyroid or eye lenses during these procedures. The aim of our study was to determine the radiation exposure of primary interventionalist's different body parts during EVAR and PTA procedures. The efficacy of a radioprotective drape was also evaluated.

During EVAR and PTA procedures, primary operator's organs are exposed to considerable radiation doses. The highest radiation doses were measured for the operator's hands in both procedures. Occupational radiation exposure can be reduced significantly using a radioprotective drape. However, the use of the drape needs caution as its misplacement could lead to higher doses for the patients and the operators.

APPENDIX:

Relevant Papers Published

Original Article

Feasibility of ischemic leg ulcer healing using percutaneous techniques: a real-life study

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Abstract

Background: Percutaneous transluminal angioplasty is established as the first-line vascular procedure in patients with lower extremity artery disease.

Purpose: We aimed to evaluate the technical and clinical effectiveness of percutaneous transluminal angioplasty in the management of ischemic foot ulcers.

Material and Methods: All consecutive patients presenting with a foot ulcer at the outpatient vascular surgery clinic of our hospital between June 2009 and June 2015 were evaluated using foot pulse assessment, ankle-brachial index, and duplex scanning. If non-invasive parameters suggested lower extremity artery disease, CT angiography and/or digital subtraction angiography were performed and a percutaneous transluminal angioplasty was carried out when feasible during the same session. All patients were followed until healing, amputation, death, or for at least two years. Short- and long-term clinical success was evaluated based on ulcer size and appearance. Patients with worsening ulcers after percutaneous transluminal angioplasty underwent bypass grafting or amputation.

Results: Percutaneous transluminal angioplasty was performed in 161 patients (100%) with stenoses $>50\%$, including cases lesions >10 cm and/or multiple/calcified lesions, 144 of which completed the study. In 88 (61.2%) patients, percutaneous transluminal angioplasty was performed in the suprapopliteal axis exclusively, in 10 (6.8%) patients in the infrapopliteal axis only, and in 46 (31.9%) in both levels. Percutaneous transluminal angioplasty was technically successful in 141 (98%) patients. After 3.1 years, the rate of healing was 68%, limb salvage 88%, overall survival 69.5%, and amputation-free survival 64%.

Conclusion: Our data suggest that percutaneous transluminal angioplasty for ischemic foot ulceration treatment is in the majority of patients feasible, effective, and safe with high rates of healing and limb salvage.

Keywords
Peripheral arterial disease (PAD), percutaneous transluminal angioplasty, angioplasty, ulcers, lower limb, ischemia

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Introduction

Lower extremity artery disease (LEAD) is a common disease leading to pronounced morbidity and mortality as well as to consumption of many healthcare and social-care resources. Major risk factors include ageing population, increasing prevalence of diabetes and its lower-limb-related complications, along with tobacco consumption (1–3). Critical limb ischemia (CLI), the most severe clinical manifestation of LEAD, may present with ischemic foot ulcers, rest pain, and gangrene (4).

Ischemic ulcers often begin as minor traumatic wounds that subsequently fail to heal because the blood supply is insufficient to meet the increased demands of the healing tissue (5). Furthermore, ischemic ulceration is potentially associated with increased

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risk for subsequent limb loss, high healthcare costs, and mortality (4).

Although surgical reconstruction was the standard of care for treating limb-threatening ischemia for nearly five decades, endovascular techniques have become an attractive therapeutic alternative for the majority of atherosclerotic lesions in patients with ischemic foot ulcers (6–10). Moreover, recent data indicate that treatment of CLI patients with an endovascular-first intervention may be associated with lower rates of major adverse cardiovascular events, surgical site infection, bleeding, unplanned reoperation, unplanned readmission, and, in general, with a substantially lower early morbidity compared to a surgery-first procedure (11).

Therefore, the aim of our study was first to evaluate the technical effectiveness of percutaneous transluminal angioplasty (PTA) in the management of lower limb atheromatous lesions in patients with ischemic foot ulceration in a real-life setting. The secondary aim was to assess the clinical effectiveness of PTA, including ulcer healing and amputation-free survival in these patients.

Material and Methods

Study population

We conducted a single-center, prospective cohort, observational study which included patients presenting with ischemic foot ulcers between June 2009 and June 2015. Inclusion criteria were an ulcer in the foot and an ankle-brachial index (ABI) < 0.9 or toe-brachial index (TBI) < 0.7, in case of incompressible tibial arteries at the level of the ankle. The exclusion criteria were: refusal to participate; refusal of PTA therapy; absolute contraindication to contrast media injection as determined by the investigator; uncontrollable coagulopathy; and unwilling or unable to provide informed consent or return for required follow-up evaluations. Revascularization was performed by endovascular means whenever feasible after an initial evaluation of all patients. Furthermore, cases in which surgical revacularization was considered as the first-line treatment were also excluded. As previously mentioned, an endovascular approach was always preferred when feasible, irrespective of the classification of the lesion according to the TASC II scheme, apart from cases of a profoundly unfavorable anatomic pattern (i.e. total occlusion of the infra-renal aorta and common and external iliac arteries bilaterally, total occlusion of the SFA throughout its length by severely calcified plaques and concomitant extensive atherosclerosis and occlusion of the femoral bifurcation, extensive infra-popliteal occlusion of all three tibial vessels with no run-off in the foot).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written informed consent and ethical approval was granted by our Hospital Ethics Committee.

Patient assessment: data collection

All patients underwent a detailed evaluation that included age, body mass index (BMI), past medical history (including co-morbidities, smoking history, and alcohol intake) previous management, referral, ulcer characteristics, and laboratory investigations. Preoperative evaluation included foot pulses assessment, ABI or TBI, and duplex scanning. The same multidisciplinary team was involved in assessment of all lesions. Physical examination of the foot was performed not only at inclusion, but also regularly during the study by our multidisciplinary team.

If non-invasive parameters suggested LEAD, we performed computed tomography (CT) angiography or digital subtraction angiography (DSA) and arranged the endovascular procedure based on angiographic findings. In cases where diagnostic DSA was performed, endovascular revascularization was carried out during the same session when feasible. Evaluation of the short- and long-term clinical success of the procedure was based on ulcer size and appearance.

Definition of tissue healing time was the time needed for complete epithelialization of ischemic lesions. Local wound care was also used, depending on the character of each lesion. Patients with two or more concurrent lesions were represented by the one with the worst outcome. Patients with three or more ulcers on the same foot were considered as having multiple ulcers. Ulcers were classified as: grade 1 = superficial; 2 = penetrating to tendon or capsule; or 3 = penetrating to bone and joint; and stage C = ischemic; or D = ischemic – infected; according to the University of Texas Wound Classification (13). Patients with worsening ulcers after PTA underwent bypass grafting or amputation. Major amputations were equivalent to non-healed tissue lesions. Patients with non-healed tissue lesions one month before death were considered non-healed.

We identified amputations below the ankle as "minor" and amputations through and above the ankle as "major." "Limb salvage" was achieved in case of avoidance of a major amputation during the follow-up period.

Technique

The main goal of the angioplasty (defining technical success) was to achieve straight-line flow (SLF) from

the aorta down to either a patent dorsalis pedis or distal posterior tibial artery supplying the plantar arch. The definition of technical success also included creation of SLF from the aorta to a peroneal artery that supplies either a patent dorsalis pedis or distal posterior tibial via collateral reconstitution.

All patients received PTA-first as the primary form of treatment. They also received medical therapy for risk factor modification. Hypertension definition included office systolic blood pressure (SBP) values ≥140 mmHg and/or diastolic BP (DBP) values ≥90 mmHg. All LEAD patients received statin therapy and target was set according to concomitant co-morbidities (i.e. low-density lipoprotein 70 or 100 mg/dL) in accordance with recent guidelines (14,15). In a subgroup of patients, autologous platelet-rich plasma (PRP) was used with the results published elsewhere (16). All angioplasties were performed by two interventional radiologists of our department who had 1 and 10 years of experience, at the beginning of the study. Antegrade common femoral access was preferred and performed in all patients who had no or non-significant aorto-iliac disease on Doppler arterial scans. Cross-over femoral or brachial accesses were other possible approaches based on lesion location, body habitus, and physician preference. Intra-arterial unfractionated heparin 3000–5000 IU was routinely injected via the vascular sheath at the start of the procedure and intra-arterial glycerine trinitrate 200 μg was administered before all tibial angioplasties. Angled or straight 0.035-in. guide wires (e.g. Terumo Corporation, Tokyo, Japan) supported by a standard 5-F straight or curved catheter, were used to cross most femoropopliteal lesions, while smaller diameter 0.018-in. guide wires (e.g. V-18 control wire, Boston Scientific, Fremont, CA, USA; Cruiser 18, Biotronik, Zurich, Switzerland) were used to cross infragenicular lesions (17). Our typical angioplasty strategy was to attempt intraluminal crossing of the stenoses or occlusions using a combination of a 5-F curved catheter and a 0.035-in. straight or curved hydrophilic guidewire (Terumo). In case a subintimal channel was created, we switched our technique and attempted subintimal angioplasty. To facilitate intraluminal crossing of chronic total occlusions, we also used vibrational angioplasty in a subcohort of our patients (18). This is a method that uses a specially designed hand-held motorized device that produces vibrational motion to a 0.014 or 0.018 guide wire (19–21). Once the lesions were successfully crossed, our treatment strategy consisted of direct stenting of lesions prone to peripheral embolization, such as occlusions or complex stenoses in the aortoiliac axis and acute occlusions in the femoropopliteal region and primary balloon angioplasty of below-the-knee lesions (17,18,22). PTA was the preferred technique in the femoropopliteal region and stents were only placed in cases with residual stenosis > 30% or residual dissection that compromised the anterograde blood flow. No stents were placed in the infrapopliteal level. All vascular sheaths were removed 2 h after angioplasty and hemostasis was controlled by manual compression for at least 10 min. Antiplatelet therapy was administered in every case using either single or dual drug regimens.

Technical success of the endovascular procedure was accomplished when a residual stenosis < 30% was achieved with antegrade blood flow in at least one distal vessel. Adverse events were classified according to the Society for Vascular Surgery (SVS) reporting standards. Complications were described as mild, moderate, or severe and access-related, procedure-related, and systemic (23).

Follow-up

The study was designed to follow up patients for at least two years. However, follow-up stopped when the patients withdrew informed consent or were unable to complete follow-up. Furthermore, patients were recorded as lost to follow-up if no information on them was retrieved after attempt to contact them by telephone.

Post-procedure surveillance included quarterly vascular clinic visits, during which clinical improvement (e.g. wound healing, rest pain) was assessed. Follow-up was terminated in case of death or major amputation; otherwise, it continued even after complete ulcer healing.

Statistical analysis

Results are presented as mean ± standard deviation (SD) for continuous variables, if normally distributed, and as median (interquartile range) if not. For comparisons between groups, a two-tailed t-test for independent samples (for normally distributed data) or a Mann–Whitney U test (for non-normally distributed data) was used for continuous variables and the chi-square test for categorical variables. Correlation coefficients were calculated using the Pearson or Spearman's (for non-normally distributed data) correlation test for all the independent predictors of ulcer outcome. Clinically relevant variables were included as independent variables: age; gender; BMI; smoking history; diabetes mellitus; and other co-morbidities. Only variables found significant were further analyzed. Furthermore, a binary logistic regression analysis model was applied, to assess the ability of the previous variables to predict ulcer healing. P values < 0.05 were considered statistically significant. Data were analyzed using PAWP 17.0 software (SPSS Inc, Chicago, IL, USA).

Results

Patients

A total of 225 patients with ischemic foot ulceration were initially evaluated during the study period. Of them, 12 patients were excluded due to various contraindications for endovascular treatment. From the 213 remaining cases, 52 patients had a profoundly unfavorable distribution of lesions for an endovascular approach, according to the vascular team's consensus, leaving 161 (76%) patients that underwent percutaneous procedures. Moreover, 17 patients were lost to follow-up before reaching any of the study endpoints (Fig. 1). Finally, 144 patients were studied, 102 of whom (71%) were followed-up for >24 months. Baseline clinical characteristics of studied patients are presented in Table 1. Co-morbidities were common with a relatively large proportion of patients having diabetes and hypertension. Median pre-procedural ABI was 0.45 ± 0.2.

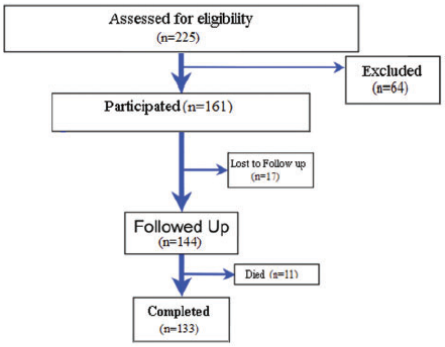

Fig. 1. Algorithm explaining the inclusion process of the patient cohort in the study.

Table 1. Baseline clinical characteristics of the final sample (only patients available for follow-up).

	Patients (n=144)
Demographics	
Age (years)	75 (16)
Male gender (n (%))	100 (69%)
Smoking status (n (%))	
Current smokers	122 (85)
Former smokers	2 (2)
Co-morbidities (n (%))	
Hypertension	111 (78)
Coronary artery disease	62 (43)
Diabetes mellitus	122 (85)
Cerebrovascular disease	18 (13)
ESRD on dialysis	6 (4)
Hyperlipidemia	65 (45)

Data are presented as median (interquartile range), unless otherwise indicated.
ESRD, end-stage renal disease.

Procedures

PTA was performed in all 144 patients. Lesion type incidence according to TASC II classification was as follows: 10 Type A; 19 Type B; 72 Type C; and 43 Type D. In 88 patients, PTA was performed in the iliofemoral axis exclusively, in 10 patients in the popliteal/tibial axis exclusively, and in 46 in both levels, with an average of 1.8 procedures per patient. One vessel was treated in 66 cases, two vessels in 45 cases, three vessels in 22 cases, and four vessels in 11 cases. Stent placements were required in 42 cases. Initial technical success was achieved in 141 cases. Technical success by type of lesion was 100% for Type A and B lesions, 98% for Type C, and 95% for Type D lesions. The ABI significantly increased post-procedurally from 0.45 ± 0.2 to 0.76 ± 0.19, $P < 0.001$.

Complications

Adverse clinical events occurred in 13 patients. One patient developed a retroperitoneal hematoma due to a high puncture, treated with a stent-graft implantation. Five patients suffered an access site hematoma requiring transfusion and six patients developed a pseudoaneurysm at the puncture site treated successfully using percutaneous thrombin injection (24,25). One patient in whom brachial access was used developed brachial artery occlusion and underwent emergency surgery.

In two patients with failure to cross an occluded SFA a femoro-peripheral bypass was performed and in one patient with iliac-occlusion recanalization failure, a femoro-femoral bypass was done. No patients died within 30 days after intervention.

Vascular re-interventions

Repeat PTA to the initially recanalized artery was performed in eight patients during the follow-up period. Eight legs were treated with a surgical bypass after late PTA failure. Presence of heart failure ($r = 0.3$, $P = 0.024$) and popliteal/tibial PTA location ($r = 0.2$, $P = 0.033$), were significant risk factors for re-intervention.

Amputations

Despite successful recanalization, minor or major amputation was required in 36 cases. Of these, 17 were major and 19 minor amputations. The need for amputation was correlated with the extent of tissue

destruction at inclusion ($r = 0.3$, $P = 0.039$). However, all had an excellent healing of the amputation stump without further complications.

Ulcer healing

In total, 98 (68%) patients healed primarily without major or minor amputation. Median time to healing was 18 weeks (range = 3–52 weeks) (Fig. 2).

Presence of hypertension ($r = -0.4$, $P = 0.015$), coronary artery disease ($r = -0.4$, $P = 0.011$), and extent of tissue destruction at inclusion ($r = -0.9$, $P < 0.001$) were associated with a lower probability of healing. Multivariate analysis identified only the extent of tissue destruction at inclusion as an independent significant factor for ulcer healing after adjustment for confounders ($P < 0.001$).

Limb salvage

The overall cumulative limb salvage rate was 88.2% at the mean follow-up time of 3.1 years. The extent of tissue destruction at inclusion ($r = 0.66$, $P < 0.001$) and the need for bypass surgery ($r = 0.3$, $P < 0.001$) significantly increased the risk of major amputation.

Survival

At a mean follow-up of 3.1 ± 1.8 years, the survival rate was 69% (44 patients died, 28 of whom from cardiac causes, eight from stroke, four from uncontrolled sepsis, and four from malignancy).

Amputation-free survival: During the follow-up period, amputation-free survival was 64%.

Amputation-free survival with healed ulcers: During the follow-up period, 62% of patients had achieved ulcer healing and were alive without a major or minor amputation.

Discussion

Our data support the technical and clinical success of PTA in the management of ischemic foot ulcers with high rates of healing and limb salvage. PTA was technically successful and feasible in almost all patients with only a minority of cases unsuitable for percutaneous techniques due to extensive and complex distribution of atherosclerotic lesions.

Another important aspect of our study is that most of the patients' lesions were classified as TASC II

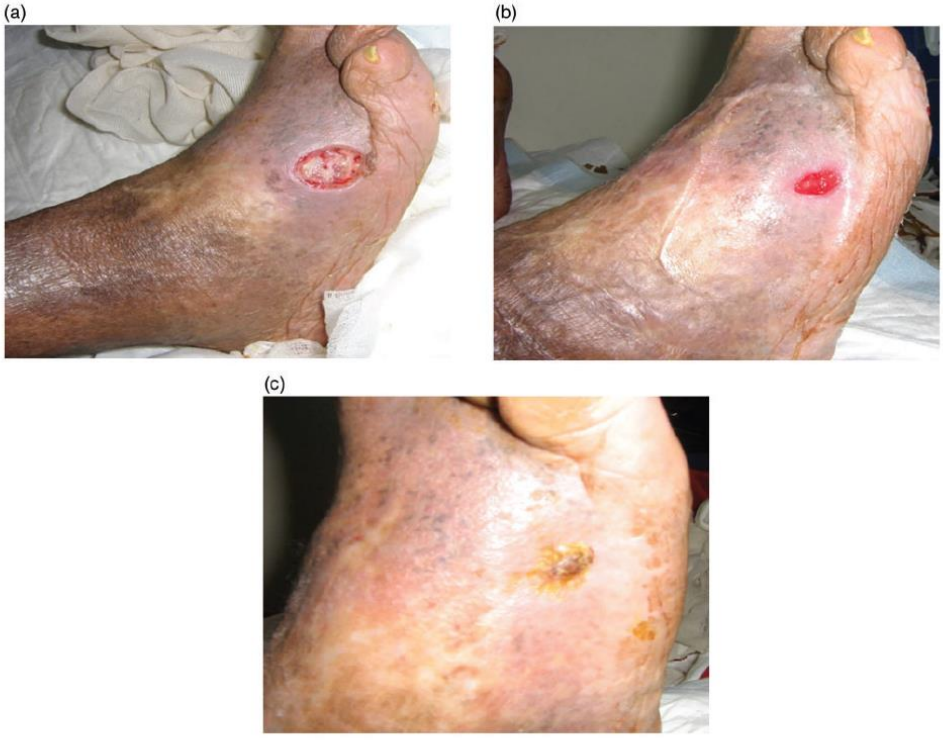

Fig. 2. Ulcer of the right forefoot (a) at presentation, (b) two weeks after PTA, and (c) eight weeks after PTA, completely epithelialized.

Type C and D, with 98% and 95% technical success, respectively, indicating that endovascular procedures can be performed in patients to whom surgical intervention was previously recommended. Therefore, our results challenge the traditional criteria for recommended treatment and also confirm previous reports (26,27) regarding clinical utility of the TASC classification system. Nevertheless, correct patient selection, operative planning performed by a multidisciplinary vascular team, and current advances and improvements in angioplasty tools and skills may have also contributed to our outcomes.

In our study, adverse events occurred in 9% of patients, mainly access-related and peri-procedural mortality was 0%, compared to a roughly 3% mortality rate and 20% major complication rate of infrainguinal bypass (28–30). Furthermore, in clinical research, the mortality rate of patients with intermittent claudication is 2.5 times higher than age-matched controls, while patients with CLI present a mortality rate as high as 20% the first year after diagnosis (4,10). Therefore, a less-invasive treatment strategy is preferable to prevent mortality especially in high-risk patients. This was the case in our study population in which, despite the relatively large proportion of diabetes and cardiovascular disease and the lower mean ABI (0.45) compared to previous studies (32), the overall survival rate was around 70% during a mean follow-up of 3.1 years. An 88% overall limb salvage rate and 64% amputation-free survival were observed, which were higher compared to previous studies in patients with LEAD and diabetic foot ulcers who did not undergo revascularization (31,32). As amputation-free survival is similar to overall survival, we could speculate that the effectiveness and durability of endovascular treatment are probably enough to meet the needs of these patients.

Our study has several clinical implications. As LEAD confers a significantly higher risk for limb loss, compared to other types of ulcers (33), aggressive attempts for revascularization with the use of percutaneous techniques may have great importance and account for these favorable results. Another important implication of the present study is that secondary interventions after an initial percutaneous approach, either by endovascular or by surgical means, had a high rate of success. In support of this, there are data suggesting that initial therapy with endovascular means does not preclude failure of secondary surgical revascularization and that feasibility of a secondary bypass and limb salvage rates are similar to the primary bypass procedure (34,35). On the other hand, data from the BASIL trial showed that patients in the endovascular group who needed a secondary bypass fared worse than those originally assigned in the surgical group (36). However, these results should be interpreted with caution, as the investigators did not focus on the question if an initial percutaneous procedure resulted in loss of outflow and subsequently precluded a surgical option. Since this was a group of a failed intervention, these cases should probably compare to the group of surgery after a prior failed surgical procedure.

Importantly, the extent of tissue destruction seems to predict worse healing over time. Delay between the onset of a foot lesion and first treatment is common and attributed mainly to underestimation of the severity of foot lesions or lack of recognition of ischemia (37). Our results underline the need to consider invasive revascularization as early as possible in patients with ischemic foot ulcers, irrespective of the presence of pain or the extent of wound. Unfortunately, assessment for revascularization in patients with ischemic foot ulcers is considered only after failure of conservative treatment (38,39).

This study has limitations that deserve comment. First, it was not a randomized trial and no control group was specified in the study design. Instead, patients served as their own controls before and after PTA. Although a matched control group receiving non-interventional therapy would be desirable for the interpretation of the effectiveness of revascularization, this was not possible due to ethical issues, especially regarding patients with more severe disease and thus possibly increased risk of amputation. Second, the anatomical success rate (i.e. vessel patency/restenosis) is not precisely known, because patients who improved hemodynamically and clinically do not routinely receive post-PTA imaging. Clinical evaluation alone was acceptable for clinical outcome, even though the same is not true for technical outcome. Third, wound care was not standardized, which might have influenced ulcer healing time. However, there is no convincing evidence that any wound dressing or local ulcer treatment method is better to promote ulcer healing process. Fourth, owing to the relatively long period studied (June 2009 to June 2015), the population was not homogeneous. Significant technical advances during the study may have biased our results. Obviously, the outcome of PTA versus vascular surgery in the present study is not directly comparable, because, according to the study design, our strategy was PTA-first with surgical reconstruction reserved for patients not amenable to PTA. Finally, 17 out of the original 161 patients were lost to follow-up (11%). This is an important study limitation, probably due to socioeconomic factors in our study sample. At the time of hospital discharge all patients were alive with no amputation, but unfortunately no further follow-up data were available.

In conclusion, endovascular intervention as the first-line treatment in patients with arterial insufficiency and

ischemic foot ulcers is feasible in the vast majority of patients and has a very high technical success rate. Percutaneous revascularization results in a high overall incidence of wound healing and limb salvage, accompanied by very low morbidity and mortality rates. Factors that affect clinical success, potentially affecting optimal treatment strategy are the extent of tissue destruction at presentation, along with patient co-morbidities.

Declaration of Conflicting Interests

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Vibrational angioplasty in recanalization of chronic femoropopliteal arterial occlusions: Single center experience

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ABSTRACT

Purpose: This prospective study aims to present the overall success rate, safety and long-term outcome of vibrational angioplasty technique, in the treatment of chronic total femoropopliteal occlusions in our institute.

Methods: Between October 2000 and December 2008, patients with chronic total femoropoliteal arterial occlusions, treated with vibrational angioplasty during the same session after a failed attempt with conventional recanalization technique, were included. Patient's follow up included serial ankle-brachial index measurements and arterial duplex ultrasound examinations at 1, 3, 6, 12, 24, 36 and 48 months.

Results: Twenty-seven patients (16 males and 11 females) and twenty-eight lesions were included in our study. Twenty-five lesions (89.3%) were successfully recanalized. Pain relief was noticed in twenty-one cases. From ten lesions with tissue loss (ulcer or gangrene) in successfully recanalized occlusions, six healed without major, or minor amputation. One non-healing amputation stump was healed after recanalization, without further complications. Four limbs underwent amputation (one minor and three major) despite successful recanalization, however all had an excellent healing of the amputation stump without further complications.

The Kaplan–Meier test demonstrated 90%, 85% and 70% amputation-free survival rate at 12, 24 and 36 months, respectively. No major or minor complications were encountered.

Conclusions: Vibrational angioplasty is a safe, effective and durable endovascular technique for the treatment of chronic total occlusions in patients with limb ischemia that would be difficult to recanalize using conventional intraluminal techniques.

1. Introduction

Peripheral arterial occlusive disease (PAOD) is the most common cause of symptomatic obstruction of the human vascular tree, affecting 12–14% of the general population and up to 20% of those over 70 years old [1]. Although the pathogenetic mechanisms that lead to PAOD are similar to those of coronary artery disease, in the peripheral vasculature and specifically in the femoropopliteal segment, chronic total occlusions (CTOs) predominate stenoses [2]. The predominance of CTOs is due to limited collaterals and to the diffuse nature of the disease [3]. Therefore, CTOs are commonly found in patients with PAOD, occurring in up to 40% of symptomatic patients [4].

The presence of CTOs typically results in critical limb ischemia and restrictive intermittent claudication. Various peripheral arterial occlusive lesions (type D and type C lesions in TASC classification) have traditionally been managed with surgical therapy. However, the increased number of patients with multiple comorbidities, severe forms of PAOD and increased surgical risk, makes percutaneous transluminal angioplasty (PTA) a useful alternative to reconstructive surgery in order to minimize potential complications and improve patient outcome [5]. Approximately one-third of femoropopliteal PTAs are currently performed in the setting of CTOs with an average of 20% procedural failure rate using traditional guidewire and balloon technology [6,7].

The causes of failure are the complexity of these lesions and the difficulty of crossing the site of occlusion with conventional

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guidewires or the inability to reenter the distal true lumen from a subintimal path. In comparison with simple stenoses and acute occlusions, recanalization of CTOs is associated with lower technical success rates, higher complication rates – such as distal embolization and perforation – longer procedural times as well as elevated radiation dose levels for patients and staff [8].

In order to overcome the challenge of treating peripheral CTOs and improve the safety and effectiveness of percutaneous revascularization, several mechanical devices and techniques have been used. The technical success rates of different methods and devices in CTO's recanalization have a range from 65% to 100% [9–13].

Vibrational angioplasty is a low-energy technique that facilitates intraluminal navigation of guidewires through resistant lesions, avoiding the damage of the collateral vessels and causing less vascular trauma. Initially it was applied successfully in recanalization of chronic coronary total occlusions [14,15]. Previously 6 patients with long femoropopliteal and 12 patients with infrapopliteal occlusions have been treated with vibrational angioplasty, with an overall success rate of 100% and 92% respectively [16,17]. However, further studies with larger patient populations are needed to determine the utility of vibrational angioplasty in peripheral CTOs. The aim of this prospective study is to report the overall success rate, safety and the outcome of vibrational angioplasty technique, in the treatment of chronic total femoropopliteal occlusions in our institute.

2. Methods

2.1. Patients and design

The study population comprised of patients with chronic total femoropopliteal arterial occlusions, which were treated with vibrational angioplasty during the same session after a failed attempt of conventional recanalization technique. The patients were enrolled in the study from October 2000 to December 2008 in a consecutive order depending on vibrational device availability (the vibrational angioplasty device was only intermittently available due to manufacturing restrictions). All subjects provided written informed consent prior to entering the study and ethical approval was granted by our Institutional Review Board. All patients were assessed for risk factors of peripheral vascular disease such as age, sex, smoking, diabetes, hypertension, hyperlipidemia, and renal function. They were also questioned for medical history of coronary artery disease and stroke.

2.2. Study inclusion criteria

1. Ischemic rest pain, ulceration, or gangrene (Rutherford category 4, 5 and 6 – Fontaine stage 3 and 4) and/or severe intermittent claudication (Rutherford category 3, Fontaine stage 2) in patients unsuitable for surgical repair due to multiple comorbidities.
2. Angiographically proven chronic total occlusions in the femoropopliteal region.
3. Previous failed attempt to cross the occluded segment with conventional intraluminal techniques that lasted at least 5 min (fluoroscopy time).

2.3. Exclusion criteria

1. Contraindication to the administration of iodinated contrast medium.
2. Acute arterial thrombosis.
3. Uncontrolled coagulopathy.
4. At least one subintimal recanalization attempt during which reentry into the distal true lumen was not achieved.

Fig. 1. Vibrational angioplasty device.

2.4. Pre-treatment angiography

All procedures were carried out in an angiographic suite with a monoplane machine (Artis FC, Siemens, Erlangen, Germany). Intra-arterial Digital Subtraction Angiography (DSA) was performed in order to document and evaluate the location and anatomic characteristics of the occlusion. Evaluation included the length of the occlusion, the presence of extended calcifications and bridging collaterals, the abrupt nature of occlusion stump and the status of distal runoff.

2.5. Vibrational angioplasty technique

All procedures were performed percutaneously through an ipsilateral antegrade common femoral approach under local anesthesia with lidocaine 1%. Following insertion of a 6 F, 24 or 35 cm long sheath – depending on lesion's level – with its tip close to the occluded segment, 5000 IU of heparin were administrated intra-arterially.

Our typical treatment strategy is to initially attempt crossing the occluded segment intraluminally using a combination of a standard 5 F straight or curved catheter and a 0.035 in. straight or curved hydrophilic guidewire (Terumo). In case the wire creates an unintentional subintimal dissection we switch our technique to a subintimal one.

During the last year we started using dedicated support catheters in combination with 0.014 or 0.018 in. guidewires. In our study population, we decided after 5 min of unsuccessful conventional intraluminal attempt to switch to vibrational angioplasty technique.

Vibrational angioplasty was performed by a hand – held motorized device, designed to impart vibrational motion to a guidewire in order to facilitate crossing of the occlusion (Fig. 1). The device accommodates guidewires of up to 0.018 in. in diameter and generates a combined reciprocal and lateral movement at the tip of the wire with a range of frequencies from 16 to 100 Hz. The duration of each activation ranged from 1 to 2 min.

Initially a conventional 0.014 in. coronary guidewire was placed through an over-the-wire balloon catheter (OTW 2.0 mm × 20 mm) in order to protrude up to 5 mm from the tip of the catheter and the back end of the wire was connected to the device. The device is able to produce a complex motion at the distal tip of the guidewire, provided that it protrudes slightly from the tip of the balloon catheter. The length of the protruding wire and the frequency of the reciprocal movement, define the characteristics of the produced motion. A shortly protruding guidewire results mainly in a reciprocal type of movement. This is particularly important, when one tries to brake the hard front of the lesion and enter the occlusion. Furthermore,

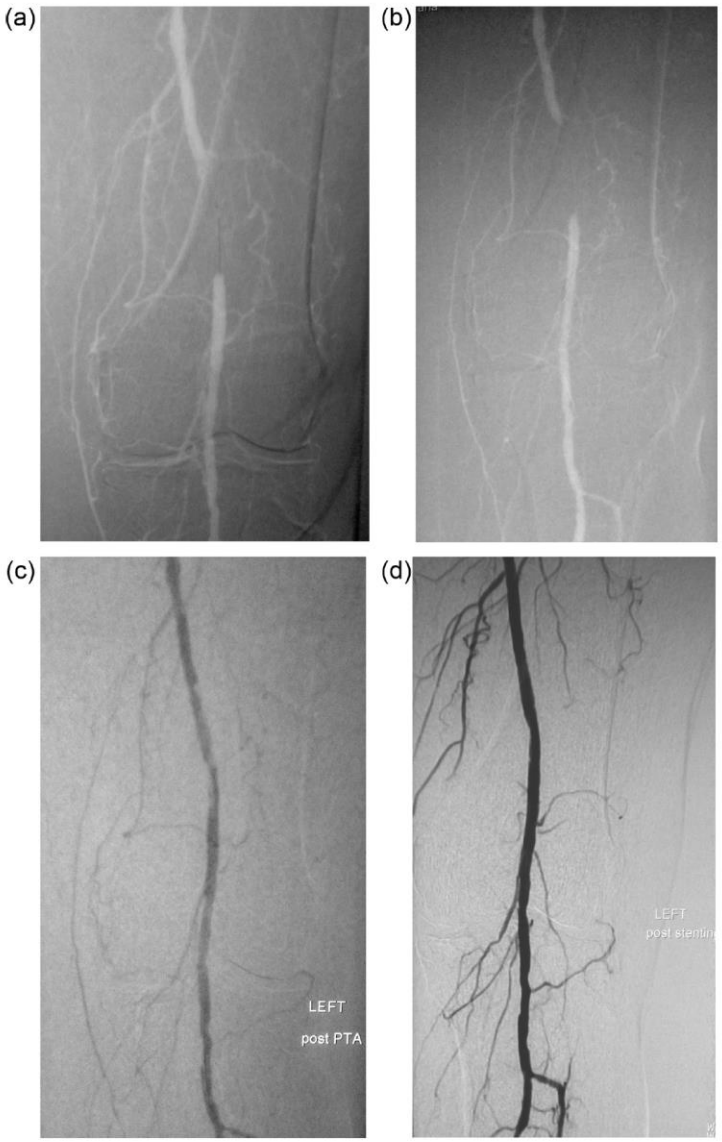

Fig. 2. Seventy-three years old male patient with restrictive claudication and poor surgical risk due to multiple comorbidities. Angiography shows a 4 cm long non-tapered occlusion of the proximal left popliteal artery which surprisingly could not be recanalized with conventional intraluminal technique. (a) The 0.014 in. guidewire tip that protrudes from the 2 mm × 20 mm balloon catheter – both of them attached to the vibrational device – has broken the front of the lesion and has almost crossed the entire occlusion. (b) The guidewire has crossed the occluded segment into the true lumen distally. (c) After balloon angioplasty an intimal flap and residual stenosis observed. (d) Stenting and final result.

during activation of the device, the operator exerts a steady forward push on the balloon catheter, in order to facilitate the penetrating effect of the reciprocal ("piston-like") component of the guide-wire movement, while the simultaneous lateral movement produced probes the occlusion for the path of least resistance. After the initial penetration of the guide wire, the protruding tip is increased up to 5 mm, resulting in a more complex movement. This movement facilitates the intraluminal navigation of the guide wire through the occlusion (Fig. 2).

We used progressively stiffer wires i.e., Hunter Soft (Abbott Ireland Vascular Division), Shinobi (Cordis Corp., Miami Lakes, FL, USA), and Crosswire (Terumo Medical Corporation, Tokyo, Japan), depending on the progress of the intervention and the characteristics of the lesion. In case of failure of the guidewire/balloon catheter

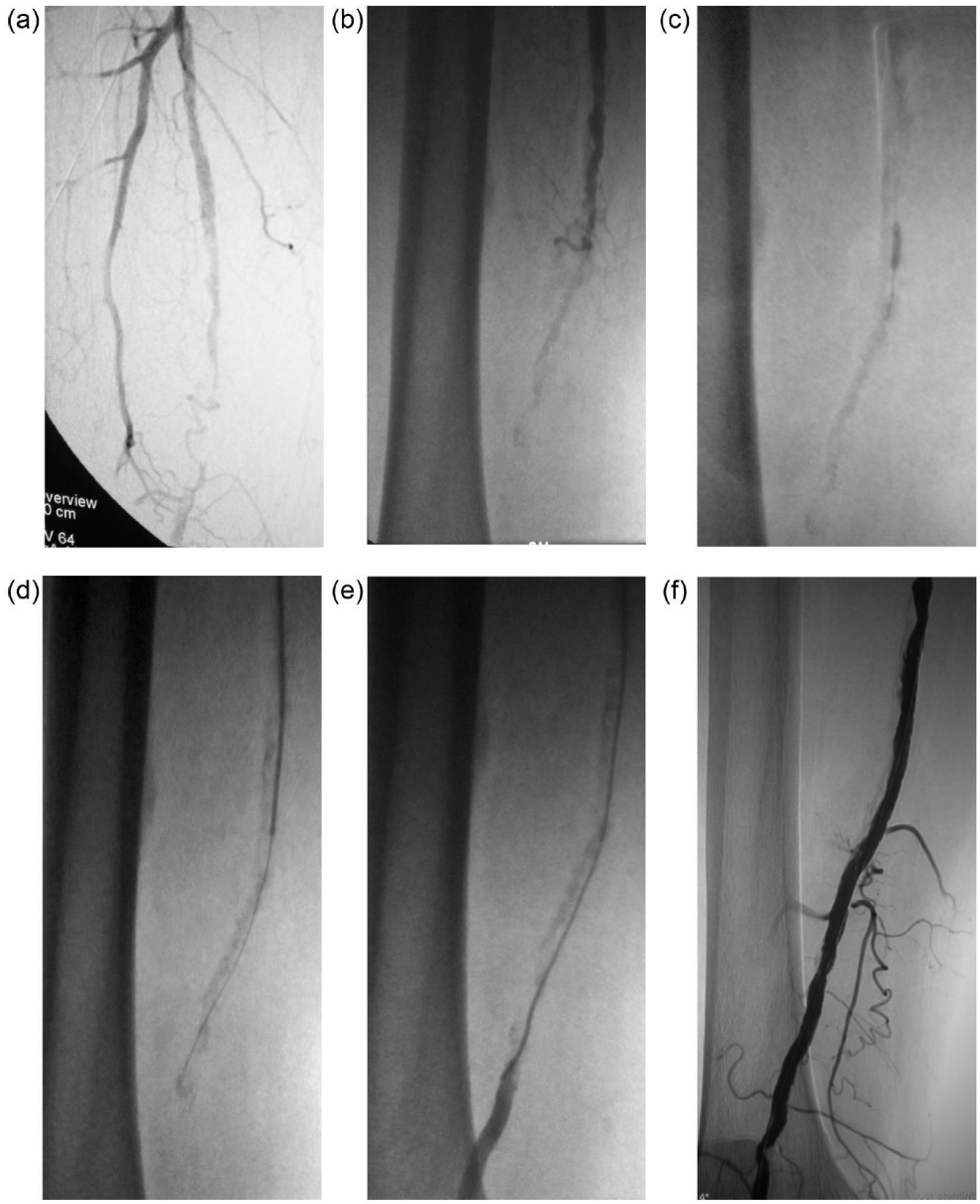

Fig. 3. Male patient with right leg critical limb ischemia. 6 cm long non-tapered occlusion of the distal SFA with heavy calcification (a). The initial 0.014 in. guidewire supported by the balloon catheter has managed to break the front of the occlusion (b). Subsequently the guidewire failed to navigate into the occlusion after the initial break, despite balloon inflation (c). A straight hydrophilic 0.035 in. guidewire was used in order to facilitate crossing the occlusion (d). The catheter has passed into the true lumen distal to the occlusion (e). Final result following PTA and stenting (f).

system to progress despite the wire's assumed intraluminal course, the balloon was inflated briefly, and the procedure was continued. Occasionally the 0.014 in guidewire was used just to brake the hard front of the occlusion in order to subsequently facilitate crossing of the lesion with a straight 0.035-in. hydrophilic guidewire. This modification of the technique was applied in heavily calcified occlusions in which navigation of 0.014 in. guidewires appeared to be impossible during the initial crossing attempts (Fig. 3). After crossing the lesion with the guidewire, contrast medium was injected to document intraluminal position. Following crossing of the occlusion, PTA was performed in the conventional way. No guide or support catheters were used during application of vibrational angioplasty technique.

Technical success was defined as complete intraluminal crossing of the occlusion followed by placement of the guidewire into the true distal lumen. Clinical success was defined as dissolution or

improvement of disabling claudication symptoms and in cases of critical limb ischemia as limb salvage, ulcer or amputation stump healing and rest pain relief. Minor complications were defined as any adverse event that required no further therapy (e.g., minor groin hematoma). Major complications were defined as any adverse event requiring further therapy or leading to prolonged hospitalization (>48 h) (e.g., retroperitoneal bleeding, pseudoaneurysm requiring thrombin injection) [18].

2.6. Follow-up

Patients follow up included serial ankle-brachial index (ABI) measurements and arterial duplex ultrasound examinations at 1, 3, 6, 12, 24, 36 and 48 months. The degree of clinical status improvement was assessed using the Society of Vascular Surgery's grading system [19]. Patients with clinical evidence of recurrent disease and typical symptoms of arterial insufficiency were scheduled for control angiography. Amputation-free survival was calculated by Kaplan–Meier life table analysis and is expressed as the percentage of survival probability with standard error.

3. Results

Twenty-seven patients (16 males and 11 females) and twenty-eight lesions (1 patient underwent a second intervention in a different segment and in a different session on the same limb) were included in our study. Patient's baseline clinical and angiographic characteristics are presented in Table 1.

Twenty-five out of twenty-eight lesions (89.3%) were successfully recanalized. Eighteen from twenty-four patients (75%) that were recanalized successfully had diabetes mellitus. All three patients that were unsuccessful had diabetes mellitus and two of them had extensive arterial calcification. Failure was due to inability of the guidewire to break the front of the lesions (10 cm and 8 cm long) in patients with extensive calcification. The third failure case was due to inability of the guidewire to cross the occlusion intraluminally after successfully entering the proximal end (6 cm long occlusion). One patient in whom recanalization failed underwent surgical treatment with femoropopliteal bypass and died a few days later from heart attack. The two other patients with failure underwent amputation. Seventeen lesions had no tapered occlusion stump and twenty lesions had extented bridging collaterals.

In four cases a straight 0.035 in. hydrophilic guidewire (Terumo) was additionally used in order to facilitate crossing of the lesion after breaking the hard front end of the lesion with a 0.014 in. wire. Time to cross the lesion with wire was estimated from 3 to 23 min (average 10.1 min). In all successfully recanalized occlusions no obvious flow limiting dissections were identified, following crossing of the lesion by the guidewire and – interestingly enough – after conventional PTA. In eleven patients stent deployment was deemed necessary due to residual stenosis following PTA. Additional balloon dilatation was performed in five cases in order to improve inflow, or outflow and ensure optimal outcome.

Pain relief was noticed in all six patients with intermittent claudication and in eight patients with rest pain. From ten limbs with tissue loss (ulcer or gangrene) in successfully recanalized cases, six healed without major, or minor amputation. One non-healing amputation stump was healed after recanalization, without further complications. Four limbs underwent amputation (one minor and three major) despite successful recanalization, however all had an excellent healing of the amputation stump without further complications.

Vibrational angioplasty results are presented in Table 2. The association of risk factors with procedural outcome is presented in Table 3. The Kaplan–Meier test (Fig. 4) demonstrated 90%, 85% and 70% amputation-free survival rate at 12, 24 and 36 months, respectively. No major or minor complications were encountered.

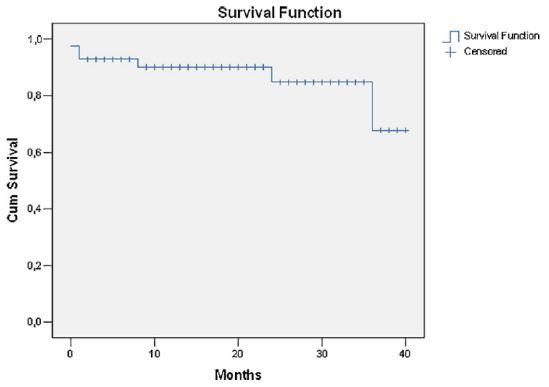

Fig. 4. Kaplan–Meier test showing amputation-free survival rate.

4. Discussion

Femoropopliteal segment is a common, challenging to treat, region of chronic total occlusive lesions. As CTOs account for a significant portion of the lesions encountered by interventionalists and one of the primary causes of procedural failure in peripheral interventions, there are concerns about the ability to recanalize safely and the long-term durability of therapy. The two ways to address CTOs currently is either intraluminal or subintimal approach, a choice that is highly dependent on personal training and expertise. Both procedures are low cost options and can provide effective CTO crossing with acceptable technical success rates [20]. Conventional catheter-supported guidewire manipulation is the most commonly used intraluminal CTO crossing method: however, it is associated with high rates of procedural failure and may require conversion to subintimal technique to achieve a technically successful crossing. In addition, it is almost impossible to know if the guidewire remains in the true lumen along entire CTO course and because of the amount of intraluminal material, adjunctive therapy may be required to debulk or modify plaque [21,22].

For conventional intraluminal CTO recanalization, a variety of guidewires (straight or angled tip configuration, full-length or only distal tip hydrophilic coating, variable tip loads, soft or stiff) are generally used with variable diameter (0.014–0.035-in.) and length (180–300 cm) depending on the point of access, operator preference, amount of calcium and the need for adjunctive tibial recanalization. The guidewires are supported by conventional standard or hydrophilic 4–5Fr catheters with various tip configurations. Recently introduced dedicated CTO support catheters have been successfully used in combination with matching guidewires of variable diameters.

Subintimal recanalization, developed by Bolia and Bell [23], is an accepted method in the treatment of CTOs with high technical success rates and high limb salvage rates in critical limb ischemia, but advanced interventional skill is required and there may be a 10–15% need for a reentry device and a substantial need for adjunctive stenting [24]. Furthermore, subintimal angioplasty carries a significant risk of collaterals damage. Collaterals comprise a physical bypass to the ischemic tissue. The combination of collateral thrombosis and the inability to re-enter into the distal true lumen can be disastrous and lead to limb loss. As a consequence many interventional centers, including ours, favor intraluminal approach as the first choice in recanalization of CTOs.

Table 1
Patient's baseline clinical and angiographic characteristics.

No sex/age (years)	Risk factors	Symptoms	ABI	Arterial location	Length, cm	Ca++	Occlusion stump	Collaterals	TASC II
F/67	DM, HYP, STROKE	Rest pain	Uncompressed	SFA-POPA ak*	10	No	Non-tapered	Yes	B
M/81	CAD, ESRD, HYP, SMK	IC	0.39	SFA mid	6	Yes	Non-tapered	Yes	B
M/74	CAD, DM, HYP	Non healing amputation	0.3	POPA*	3	Yes	Tapered	No	C
M/73	HYP, SMK, HRL	Ulcer	0.4	SFA dist-POPA ak*	8	No	Tapered	No	A
M/75	CAD, DM, SMK	Gangrene	0.19	SFA dist	6	Yes	Non-tapered	Yes	B
F/92	DM, HYP	Ulcer	Uncompressed	POPA-ak	3	No	Non-tapered	No	B
F/61	CAD, SMK, HYP, HRL	IC	0.26	SFA prox	10	Yes	Non-tapered	No	B
M/69	DM, SMK, HYP	Rest pain	0.3	POPA-ak	4	Yes	Non-tapered	No	A
M/52	DM, SMK, HRL	IC	0.6	SFA mid-distal	10	No	Non-tapered	Yes	B
F/83	CAD, DM, HYP	Ulcer	0.4	SFA dist, POPA-	10	No	Non-tapered	Yes	B
M/71	CAD, DM, ESRD, HYP, SMK	Ulcer	Uncompressed	SFA prox	10	Yes	Non-tapered	No	B
F/72	DM, HYP	Ulcer	Uncompressed	POPA ak	6	No	Tapered	Yes	B
F/75	CAD, DM, HYP	Gangrene	0	SFA-POPA ak	8	Yes	Tapered	Yes	B
M/84	DM	IC	Uncompressed	SFA dist	8	No	Non-tapered	Yes	B
M/75	DM, CAD, STROKE	Rest pain	Uncompressed	SFA dist	3	No	Tapered	No	A
M/93	HYP, SMK	Rest pain	0.41	dist SFA-POPA, ak	6	No	Non-tapered	Yes	B
F/80	HYP, HRL	IC	0.32	POPA-ak	4	No	Tapered	No	A
F/77	CAD, DM, HYP	Rest pain	Uncompressed	POPA*	5	Yes	Non-tapered	Yes	B
F/75	DM, CAD, HYP	Rest pain	Uncompressed	POPA-bk	4	No	Tapered	Yes	A
M/73	HYP, SMK, HRL	IC	0.25	POPA-ak	4	No	Non-tapered	Yes	A
M/82	DM	Gangrene	0.2	SFA prox.	6	No	Non-tapered	Yes	B
F/75	DM, CAD	Ulcer	0.2	SFA prox.	10	No	Non-tapered	Yes	B
F/77	HYP, HRL	Gangrene	0.1	POPA	4	No	Non-tapered	Yes	B
M/67	DM, HYP, SMK	Ulcer	0.3	POPA	4	No	Non-tapered	Yes	B
M/53	DM, HRL, HYP, CAD, SMK	Gangrene	Uncompressed	SFA	4	Yes	Tapered	Yes	B
M/57	DM, HRL, CAD, SMK	Rest pain	0.3	POPA	3	Yes	Tapered	Yes	B
M/71	DM, CAD	Ulcer	0.3	POPA	3	Yes	Tapered	Yes	B
M/70	DM, HYP, CAD	Rest pain	0.5	SFA dist-POPA ak	5	Yes	Tapered	Yes	B

CAD, coronary artery disease; DM, diabetes mellitus; ESRD, end stage renal disease; f/m, female/male; HRL, hyperlipidemia; HYP, hypertension; IC, intermittent claudication; POPA ak, popliteal artery above knee; POPA bk, popliteal artery below knee; SFA, superficial femoral artery; SMK, smoking; TPT, tibioperoneal trunk; *, in-stent restenosis.

Table 2
Vibrational angioplasty results.

Technical success	Crossing time	ABI	Pain relief	Amputation	Healing	Additional dilation
Yes	19 min	Uncompressed	Yes	No		SFA before lesion
Yes	12 min	0.85	Yes	No	–	No
Yes	3 min	0.65	Yes	–	Yes	No
Yes	15 min	0.57	Yes	No	Yes	No
Yes	10 min	0.75	Yes	Yes (minor)	Yes	No
Yes	5 min	Uncompressed	Yes	No	Yes	No
Yes	17 min	1.0	Yes	No	–	No
Yes	6 min	0.7	Yes	No	–	No
Yes	18 min	0.8	Yes	No	–	No
Yes	20 min	0.65	Yes	No	Yes	No
No	–	–	Failed	– (Death)	No	–
No	–	–	Failed	Yes (minor)	–	–
No	–	–	Failed	Yes (major)	–	–
Yes	16 min	Uncompressed	Yes	No	–	Yes
Yes	8 min	Uncompressed	Yes	No	–	No
Yes	9 min	0.5	Yes	No	–	No
Yes	6 min	0.45	Yes	No	–	No
Yes	10 min	Uncompressed	Yes	No	–	Yes
Yes	7 min	Uncompressed	Yes	No	–	No
Yes	5 min	0.46	Yes	No	–	No
Yes	12 min	0.2	–	Yes (major)	Yes (stump)	No
Yes	23 min	0.6	Yes	No	Yes	No
Yes	5 min	0.7	–	Yes (major)	Yes (stump)	No
Yes	5 min	0.85	Yes	No	Yes	Yes
Yes	8 min	Uncompressed	–	Yes (major)	Yes (stump)	No
Yes	3 min	1.0	Yes	No	–	No
Yes	4 min	0.7	–	No	Yes	No
Yes	7 min	0.7	Yes	No	–	Yes

Table 3
Risk factor association with procedural failure.

Risk Factors	*N* (all patients)	%	*N** (failed-3pts)	%	*p*-Value
CAD	15	55.5	2	66.6	NS
DM	20	74.0	3	100	NS
SMK	12	44.4	1	33.3	NS
HYP	20	74.0	3	100	NS
HRL	8	29.6	0	0	NS
ESRD	2	7.4	1	33.3	NS
STROKE	2	7.4	0	0	NS

NS, non-significant.

During the last decade many different techniques and devices, either intraluminal or extraluminal have been developed for the treatment of CTOs [9,25]. Devices such as the Crosser (Bard Peripheral Vascular, Inc., Tempe, AZ USA), Frontrunner XP (Cordis Corp., Miami Lakes, Florida, USA), Wildcat (Avinger, Redwood City, CA), SafeCross Radio Frequency (Spectranetics Corporation, Colorado, USA) and Excimer Laser Angioplasty (Spectranetics Corporation, Colorado, USA), have been specifically designed to consistently recanalize CTOs by the intraluminal way. The Pioneer Catheter (Medtronic Vascular) and the Outback Catheter (Cordis) are typically extraluminal devices. As it is almost impossible to be competent and really comfortable with all of the crossing devices in the market, it is likely that interventionists will continue to use the technique they consider most efficacious based on their own experience. Many of these methods have been shown to be safe and effective in crossing CTOs. Nevertheless, it is still not clear if a specific technique, or device affects patency, or limb salvage rates. No approach has proven superior over the others until now [8].

Vibrational angioplasty, a technique initially presented in 1993 [26] is an effective, user-friendly method that facilitates the passage of a guide wire through the real lumen, in order to avoid subintimal dissection of the arterial wall. This is achieved by a combined reciprocal and lateral movement of a low profile guidewire, slightly protruding from the tip of a balloon catheter, a movement produced by a hand-held external generator. It was first studied in an animal model, with greater crossing success and no perforations compared to manual wire manipulation [27]. The effectiveness and safety of the method has already been demonstrated in difficult chronic coronary occlusions [15,28], with higher crossing success and less severe dissections than conventional hydrophilic guidewires [28]. Interestingly enough, only 1 perforation (without clinical consequences) has been encountered so far in all clinical studies in which this method was applied. The lower degree of vessel trauma could be explained by the nature of vibrational movement of the wire which results in more frequent but less severe contact between the wire and the vessel wall because each individual contact time is very short; this theory is supported by the less extensive and less severe damage caused by a vibrating guidewire versus conventional guidewire manipulations in normal sheep coronary arteries [29]. The advantage of this method is that the intraluminal course avoids the risk of bridging collaterals thrombosis and produces less wall trauma than the subintimal passage. Furthermore, vibrational angioplasty, as a low energy technique in combination with low profile guidewires can avoid extended wall injury that may lead to higher rates of hyperplasia and restenosis.

The preliminary results of this technique in a group of patients with femoropopliteal and infrapopliteal CTOs were promising [16,17]. Initially, vibrational angioplasty was applied to successfully recanalize chronic total occlusions in the SFA or popliteal artery in 6 patients, with no complications and a follow up ranging from 3 to 9 months, during which time all arteries were patent on duplex ultrasound imaging [16]. After the positive preliminary results the

method was applied in thirteen patients with chronic total occlusions. Twelve of these patients were successfully treated and one failed because of wall perforation with no long-term clinical sequelae [17]. The follow up in this study ranged from 1 to 18 months, during which time none of the patients experienced hemodynamic deterioration.

The present study includes a larger number of patients and longer follow-up time, demonstrating the efficacy as well as safety of vibrational angioplasty technique in the treatment of CTOs. There were no major complications and no angiographically visible trauma, or dissection was noticed. As it results from the relevant Kaplan Meier curve, vibrational angioplasty is a method with significant contribution in amputation free survival of the patients with critical limb ischemia. This is of great importance, because amputations result in increased rates of morbidity and mortality, increased cost and poor quality of life. As most of these patients have decreased life expectancy, it is obvious that the extension of free amputation time may offer them a free amputation life. In our study, only 4 patients needed amputation despite successful recanalization, but they ultimately had a complete and uncomplicated healing of the stump.

Our study has some limitations that deserve comment: first, the sample size was relatively small, because the vibrational angioplasty device was only intermittently available due to manufacturing restrictions. Second, the study population was non-randomized, and no control group was specified in the study design. Third, the mean lesion length was relatively short, due to the fact that we included a considerable number of popliteal lesions < 5 cm in length in whom we were reluctant to insist on recanalization by conventional techniques due to the fear of a disastrous dissection. Lastly, since we tried this technique only in cases in which an initial intraluminal attempt by conventional means failed, we cannot evaluate the real success rate of this technique in de novo patients.

In conclusion, vibrational angioplasty is a safe, effective and durable endovascular technique for the treatment of chronic femoropopliteal total occlusions in patients that would be difficult to recanalize using conventional techniques.

Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Effectiveness of Platelet-Rich Plasma to Enhance Healing of Diabetic Foot Ulcers in Patients With Concomitant Peripheral Arterial Disease and Critical Limb Ischemia

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Abstract

We sought to investigate the effect of autologous platelet-rich plasma (PRP) on the healing rate of diabetic foot ulcers in patients with diabetes and concomitant peripheral arterial disease (PAD). Diabetic patients with foot ulceration presenting with PAD who were treated with local growth factors in a single center, during a 24-month period from May 2009 to April 2011, were retrospectively reviewed. Based on the severity of PAD, subjects were divided into groups A (Fontaine classification stages I, IIa, and IIb) and B (Fontaine classification stages III and IV), with those included in the latter being considered to suffer from critical limb ischemia (CLI). End points of the analysis were clinical improvement, limb salvage, and amputation rate. Outcome was compared between groups A and B. Overall, 72 patients were evaluated, 30 with CLI. Ulcer area reduction >50% was observed in 58/72 patients while reduction >90% was achieved in 52/72 patients. There were 14 (19%) major and minor amputations, whereas the limb salvage rate was 89%. This variable was significantly different between groups A and B (100% vs 73%, $P < .001$), as is rate of reduction in ulcer area >90% (83% vs 56%, $P = .02$). Reduction of ulcer area >50% was observed in the majority of patients in both groups (group A 86% vs group B 73%, $P = .23$). In conclusion, PRP could serve as a useful adjunct during management of diabetic foot ulcers even in diabetic patients with unreconstructable arterial disease.

Keywords

growth factors, ulcer healing, limb salvage, amputation rate

Diabetes is a major health problem that is currently showing an alarming rise in its prevalence. This has recently been estimated at 7.8% in the United States, presenting a >50% increase over the past 15 years while there exists a large population group in whom diabetes is undiagnosed.[1] Diabetic foot ulceration (DFU) is an unavoidable event during the clinical course of many patients, up to 25% of whom will suffer from a foot ulcer during their lifetime.[2] Approximately 20% of these ulcers ultimately require amputation and 85% of all diabetic lower limb amputations are preceded by an ulcer.[2] It is worth noting that these patients are 15 to 30 times more likely to undergo an amputation than those without diabetes.[3,4]

The pathophysiology of DFU lies on the mixed effects of sensory, motor, and autonomic neuropathy along with abnormal foot mechanics, structural deformities, microvascular angiopathy, and compromised immune system. The aforementioned factors often coexist with peripheral arterial disease (PAD), which compromises perfusion on a macrovascular level having a substantial deteriorating effect and indicating a worse prognosis.[5,6] The true prevalence of PAD in diabetic patients has been difficult to determine because pain perception may be blunted in many of them while others due to a poor general status undertake only minimal physical activity in their daily practice, which is not enough for ischemic symptoms to develop. Accordingly, diabetic patients with PAD are more likely than nondiabetic patients to present advanced disease at initial diagnosis, often with an ulcer and critical limb ischemia (CLI) as the first symptoms.[7] In many modern series, a high prevalence of diabetes among subjects undergoing revascularization for limb salvage is reported ranging from 50% to

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80%. This was 58% in the BASIL trial, 64% in the PREVENT III trial, and exceeds 70% to 80% in many specialized vascular centers.[8-13]

To maximize potential for wound healing, a multidisciplinary approach is needed, involving off-loading, regular wound debridement, ultimate control of gangrene or sepsis, antibiotic therapy, negative-pressure wound therapy, and sometimes skin grafting, while glycemic control is of paramount importance. However, these therapeutic measures can succeed only in the presence of adequate arterial perfusion. Subsequently, aggressive attempts for revascularization are indicated as one of the first and most important measures to enhance ulcer healing and maximize possibilities for limb salvage.[14] Therefore, endovascular and surgical techniques are being employed in this regard, to provide adequate blood flow and restore oxygenation in an effort to allow inflammatory and proliferative tissue response, necessary for ulcer healing to take place. Nevertheless, it is not rare that these patients are not suitable for such interventions since the unique anatomy of occlusive disease in diabetic patients, which mainly involves arteries distal to the popliteal, sparing more proximal segments of the arterial tree, often precludes any kind of revascularization. Unreconstructable vascular disease has become the most common indication for primary or secondary amputation, accounting for nearly 60% of patients.[15] Moreover, a significant proportion of patients with diabetes may present significant comorbidities, thus not being good surgical candidates to undergo lengthy, complex, and repetitive surgical procedures. Therefore, restoration of arterial perfusion is not always an option and in this scenario amputation is a frequent outcome.

The use of growth factors (GFs) as an adjunct to enhance tissue remodeling and promote ulcer healing has been extensively studied in the literature. The rationale for their use lies on their contribution on the biological events that take place during the healing process.[16,17] Various research studies have suggested a therapeutic potential of externally applied GFs in patients with impaired wound healing generally by achieving better healing rates, reducing ulcer volume and area, and decreasing time to complete healing.[18-25] Nevertheless, studies investigating the possible gain of such interventions generally have treated lower limbs with adequate arterial perfusion, having excluded those with PAD, which, as mentioned previously, can be the case in a significant proportion of this population.[24-26]

In the current study, we attempted to examine the efficacy of autologous platelet-rich plasma (PRP) for the treatment of DFU in patients with concomitant PAD. Subjects in the most severe spectrum of arterial disease, meaning those with CLI, were also included. In this regard, our research aims to investigate whether GFs could also serve as a useful adjunct for ulcer healing in patients with diabetes and concomitant unreconstructable arterial disease or those who would not be good surgical candidates and otherwise would most likely have ended up with a major amputation.

Methods

Study Design

This is a single-center, retrospective study including patients treated during a 24-month period from May 2009 to April 2011. Institutional review board approval was obtained for the current study. Eligible subjects were those meeting the following inclusion and exclusion criteria.

Inclusion Criteria

- Type 1 or 2 diabetes controlled by either medication or insulin.
- Presence of a foot ulcer for at least 4 weeks to be considered chronic.
- Diabetic foot ulcers that are clinically noninfected. A culture was obtained but generally infection was diagnosed through clinical signs and symptoms.[27]
- According to University of Texas Treatment-Based Diabetic Foot Classification System ulcers with wound depth 0 (pre-ulcerative lesion or healed ulcer site), 2, and 3 (wound extends to tendon, bone, or joint) were not included as well as those of class A (− Infection, − PAD), B (+ Infection, − PAD), and D (+ Infection, + PAD). Ulcers of grade 1C were included (Wounds without tendon, capsule, or bone involvement, − Infection, + PAD).[28]
- Presence of PAD as defined by an ankle–brachial index (ABI) <0.9. In patients with falsely elevated ankle pressures due to incompressible vessels at the level of the ankle, the toe–brachia index (TBI) was used and PAD was indicated by a TBI <0.7.[15] To measure ABI a 10- to 12-cm sphygmomanometer cuff is placed just above the ankle and a Doppler instrument is used to measure the systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg. These pressures are then normalized to the higher brachial pressure of either arm.[15]

Exclusion Criteria

- Purulent ulcers with severe infection and wet gangrene
- Exposure of bone, muscle, ligaments, or tendons
- Charcot's arthritis

Patients were divided into 2 groups based on the severity of PAD. Those without CLI were assigned to group A (Fontaine classification stages I, IIa, and IIb) while those with CLI were assigned to group B (Fontaine classification stages III and IV).[15]

The precise level of perfusion deficit that defines "critical ischemia" is unclear especially among patients with diabetes.[29] Nevertheless, for simplicity reasons we followed the TASC II document classification to perform the current analysis. Therefore, patients with an ankle pressure >70 mm Hg or toe pressure >50 mm Hg for those with incompressible vessels at the level of the ankle were assigned to group A, while if ankle pressure was <70 mm Hg or toe pressure <50 mm Hg, subjects were considered to suffer from CLI and they were assigned to group B. To those patients that surgical revascularization or endovascular procedures were indicated and were feasible these had been undertaken before initiation of PRP application. Median time interval from reperfusion to initiation of treatment with GFs was 21 days. Subjects included in the current analysis were judged unsuitable for any additional revascularization to be attempted. This was mainly due to multilevel, diffuse atherosclerotic disease, in the absence of distal run off vessel for arterial bypass to be feasible.

Procedures

General Measures. In both groups, wounds were initially cleansed with normal saline and moist saline gauze dressings were used. Cleansing with normal saline solution was performed gently using gauzes and/or sponges with minimum mechanical force. When required, patients had surgical debridement of the wounds before application of GFs to freshen the wound bed and remove all necrotic tissue. Cultures were taken at that time. All patients were advised to undertake offloading in order to relieve pressure on ulcers. This was always performed using therapeutic shoes or in-shoe orthoses, while casts and/or surgical offloading was not used in any case in this series. There is a general consensus regarding use of footwear and offloading techniques for the prevention and healing of plantar foot ulcers in diabetic patients by reducing plantar pressure at sites of ulceration. The mechanical effect of special footwear is thought to rely on plantar pressure reduction over the at-risk area and a transfer of load to other regions.

To relieve pain, usually oral paracetamol was prescribed with the addition of opioids (drops tramadol) when the patient could not tolerate pain, while need for analgesics tended to decrease along with ulcer healing. Overall, any type of analgesics were required in less than half of our patients, which is believed to be due to reduced pain perception in diabetic patients with severe sensory deficit.

Taking into account that subjects included in the current study by definition suffered from PAD, all patients were on antiplatelet agents. Usually, single antiplatelet regimens with aspirin were preferred while clopidogrel was also used in some instances (ie, allergic reactions in aspirin as a single therapy or dual antiplatelet therapy on patients with recent cardiac interventions). Statins were also prescribed in the majority of cases.

PRP Preparation and Application

- The RegenKit-ATS (RegenLab, Le Mont-sur-Lausanne, Switzerland) system was used for autologous PRP preparation. This contained one safety-lock butterfly needle, one collection holder, the RengenATS tubes and a pair of sterile pliers.
- Two to 4 tubes were filled with the patient's venous blood depending on the ulcer size. The vacuum within the tube enabled automatic collection of the necessary volume of blood (about 8 mL for each tube).
- The blood tube is then immediately centrifuged for 8 minutes to 3000 rpm, which allows blood separation into 2 layers, namely, bottommost red blood cell layer (55% of total volume) and topmost PRP plasma layer.
- After the centrifugation plasma was allowed to clot ex vivo to form a platelet-rich fibrin clot. If the formation of the clot is not immediately observed the tubes were kept standing and let to rest for a few minutes (usually 3-5 minutes).
- The sterile pliers included in the set were then inserted to the base of the clot along the tube walls. With a circular movement of the pliers against the wall, the clot was carefully unstuck and extracted.
- PRP is then applied on the ulcer area.
- A small amount of plasma (1-2 mL) was usually presented into the tube after removing the PRP, which was mainly in a semiliquid condition compared to the previously removed PRP gel. This was also placed on the bed of the ulcer using a sterile syringe. The bottommost red blood cell layer is then discarded.
- Then the area was covered with a moist saline gauze dressing.

PRP application was performed twice a week. Length and width measurements were performed at each visit and area was calculated from these measurements (Length × Width). Photos of the ulcer were taken with a digital camera at that time. Therapy was discontinued either after complete ulcer healing, application of PRP for 16 weeks, or if no or very low progress was observed after 3 continuous sessions. The aforementioned preparation and application of PRP has been previously described with some modification in the literature.[30,31] There were no complications from application of GFs observed in this series.

Endpoints and Statistical Analysis

The main endpoints of the current analysis were ulcer healing or improvement, avoidance of an amputation, and limb salvage.

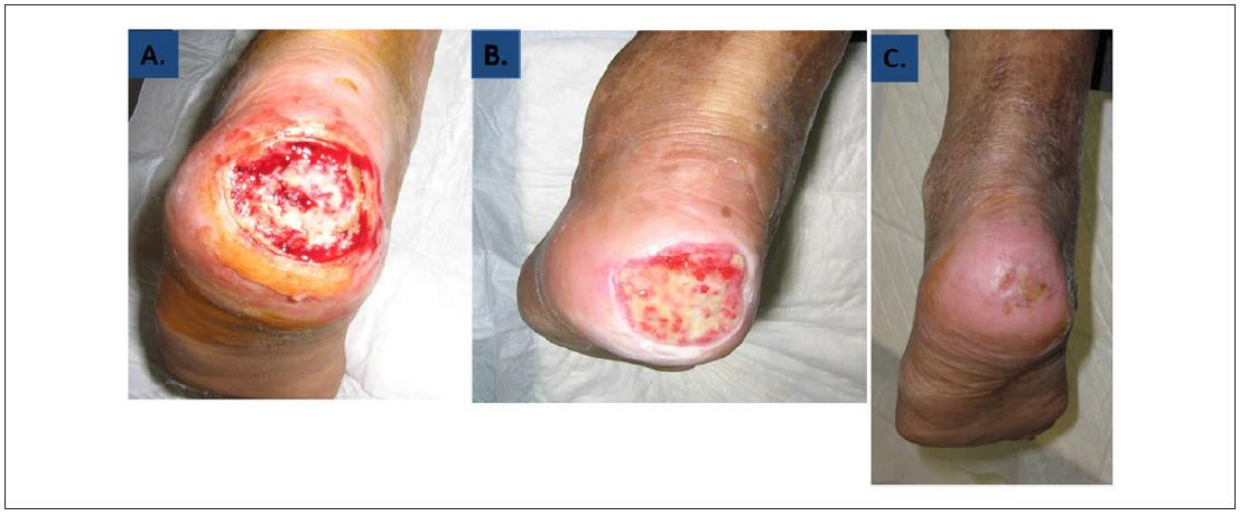

Figure 1. A representative case of foot ulceration in a diabetic patient being assigned to group A (compromised arterial perfusion without CLI). (A) Initial presentation, (B) After session 6, (C) Complete wound healing after session 15.

With regard to clinical outcome, ulcers were characterized as follows:

1. Significantly improved ulcers (ulcer area reduced >90%)
2. Moderately improved ulcers (ulcer area reduced 50% to 90%)
3. Nonimproved ulcers (ulcer area reduced <50%)

Limb salvage according to "Recommended standards for reports dealing with lower extremity ischemia" is applied to therapeutic outcome of interventions intending to avoid a major amputation. The designation "minor amputation" would require retention of a functional foot remnant to allow standing and walking without a prosthesis, which would include toe or transmetatarsal amputations, with most high forefoot amputations as well as below and above knee amputations being included under "major amputations" and fall out of the definition of limb salvage.[32]

The aforementioned endpoints were assessed for all patients under evaluation. Rates of ulcer healing, avoidance of an amputation, and limb salvage were recorded for our study population as a whole. Moreover, the same variables were assessed for groups A and B. Statistical significance of differences between groups was evaluated using χ^2 test.

Results

Patient Characteristics and Overall Data

Overall, 72 patients were eligible to be included in the current analysis. There was no loss to follow-up for the patients included in the current analysis. Although majority of cultures obtained from the wound during patient's initial presentation indicated the presence of microorganisms, mainly aerobic gram-positive cocci particularly staphylococci species and scarcely aerobic gram-negative bacilli and anaerobes, most of this is believed to be colonization since it has been suggested that the presence of infection should be primarily determined on the presence of clinical findings.[27] Despite the fact that some debridement was initially required in the majority of ulcers treated in our series (57/72% to 79%) this was always minor.

According to ankle and/or toe pressure measurements, 42 subjects were assigned to group A and 30 patients to group B. Mean age was 65 years and there was a male-to-female ratio of 4:1. Regarding group A, mean systolic blood pressure at the level of the ankle was 98 ± 18 mm Hg and mean ABI was 0.75 ± 0.13. Corresponding values for group B were 48 ± 8 mmHg and 0.35 ± 0.09. Baseline mean ulcer area of all the 72 patients included in the current analysis was 4.1 ± 3.9cm^2 (mean ± standard deviation). Overall, the ulcer was significantly improved (ulcer area reduction >90%) in 52 patients (72%) within an average of 11 ± 4 sessions. A representative case of complete ulcer healed is presented in Figure 1. In 6 (8%) of our patients the ulcer was moderately improved (ulcer area reduction between 50% and 90%) within an average of 12 ± 4 sessions. In 14 (20%) of the patients there was no benefit from therapy and subsequently they underwent 6 minor and 8 major amputations (20% amputation rate). Limb salvage (avoidance of a major amputation) was achieved in 64 out of 72 limbs treated (89%).

Comparisons Between Groups

Debridement was initially required in 34/42 (81%) patients in group A and in 23/30 (77%) in group B. Since initial debridement was always minor, it did not affect observed

Table 1. Overall Results and Comparisons Between Groups Are Presented[a].

	Ulcer Area Reduction >50%	Ulcer Area Reduction >90%	Any Amputation	Limb Salvage
Group A (n = 42)	36 (86%)	35 (83%)	6 (14%)	42 (100%)
Group B (n = 30)	22 (73%)	17 (56%)	8 (27%)	22 (73%)
Statistical significance	$P = .23$	**$P = .02$**	$P = .23$	**$P < .001$**

[a]The third column (Any Amputation) refers to both minor and major amputations (nonsignificant differences between groups A and B). The fourth column (Limb Salvage) refers to the avoidance of a major amputation while minor amputation would qualify for limb salvage (limb salvage significantly more common in Group A). Although limb salvage and ulcer healing >90% are significantly more common in group A, results in group B may also represent a quite favorable outcome for these patients. P-values in bold characters indicate statistical significant differences.

results as expected. Comparison of baseline mean ± standard deviation ulcer area between groups A (4.2 ± 3.9 cm^2) and B (3.8 ± 3.5 cm^2) indicated nonsignificant differences ($P = .82$). With regard to clinical improvement (ulcer area reduction >50%), there were 36/42 (86%) improved ulcers in group A and 22/30 (73%) in group B, and this difference was not statistical significant ($P = .23$). Rate of ulcer area reduction >90% was significantly higher in group A (35/42% to 83% vs 17/30% to 56%, $P = .02$). Regarding need for an amputation, there were 6/42 (14%) amputations in group A and 8/30 (27%) in group B, and the difference was not again statistically significant ($P = .23$). Finally, regarding rate of limb salvage there was no limb loss in group A (limb salvage 42/42, 100%) and 8 limb losses in group B (limb salvage 22/30, 73%). Limb salvage was significantly greater among patients in group A ($P < .001$). These results are summarized in Table 1.

Discussion

Diabetic foot ulcers represent a major cause of morbidity between diabetic patients that can seriously impair quality of life and often result in limb loss. GFs have been suggested to be a useful adjunct in order to achieve ulcer healing in these patients. These are biologically active polypeptides that act to alter the growth, differentiation, and metabolism of target cells stimulating cellular proliferation, chemotaxis, and angiogenesis.[33]

The potential benefits of GFs in the treatment of chronic wounds have been suggested by many investigators. Saad Setta et al performed a randomized trial to compare the effects of platelet-rich and platelet-poor plasma (PRP and PPP), respectively, in ulcer healing demonstrating that this was significantly faster in the PRP group.[30] Anitua et al measured the mean percentage of ulcer surface area healed in their study population, which was 72.94% in patients treated with GFs versus 21.48% in those receiving standard care, a difference that was statistically significant.[31] Steed studied the effects of topical recombinant human platelet–derived GF compared with placebo. They included 118 patients and suggested that the group treated with GFs achieved a significantly higher healing rate (48% vs 21%) while the median reduction in wound area was also significantly greater in the former group (98.8% vs 82.1%).[20] Wieman et al indicated that becaplermin significantly increased the incidence of complete wound closure when compared with placebo and decreased the time to achieve complete wound closure in a study of 379 patients.[21] Data from randomized trials suggest amputation rates as high as 45% in patients with DFUs when treated with a standard care protocol while this was significantly less (15%) for those treated with GFs. These results are broadly similar with those presented in this report (overall amputation rate 19%) despite the fact that unlike previous research we evaluated patients with concomitant PAD.[19] Others report complete healing rates of only 35% for diabetic patients receiving standard care, indicating an overall unfavorable prognosis for these lesions.[21] Moreover, a recent randomized trial found a quite similar healing rate (81.3%) when compared with our results (72%) for patients treated with PRP in the same time that significantly fewer patients in the control group (42.1%) presented complete wound healing.[25]

The above-mentioned studies indicate the effectiveness of local application of GFs to promote tissue repair and enhance ulcer healing. Nevertheless, they all have excluded patients with PAD. In the current study, we concentrate on this particular subpopulation of diabetic patients since they may face a worse prognosis and a higher possibility for an amputation. Our findings indicate good results of PRP regarding ulcer improvement in subjects with PAD. An overall >90% ulcer area reduction was achieved in 72% of patients, which reached 56% in those with CLI (group B). Improvement of the ulcer, meaning >50% reduction in the ulcer area, was achieved in 80% of our study population, while the corresponding value for group B was 73%. Limb salvage was 100% in group A, which was significantly higher than that of 73% in group B. Nevertheless, a 56% rate of significantly improved ulcers and a 73% limb salvage rate in patients with CLI probably represent a quite favorable outcome. As mentioned before, it should be emphasized that mean systolic blood pressure at the level of the ankle was 48 mm Hg and mean ABI 0.35 in this group of patients. These data allow to suggest not only a significant positive effect of PRP to enhance DFU healing, but also its effectiveness in patients with compromised arterial blood flow.

The present results should be evaluated in light of some limitations, which mainly regard the fact that the analysis was retrospective and it did not include a control group. Nevertheless, the fate of subjects with diabetes and foot ulceration is mostly well-defined since there is a considerable amount of information in the literature indicating an overall unfavorable prognosis for these patients.[2-4] More important, fate of the limb of diabetic patients with unreconstructable arterial disease has also been evaluated and limb salvage as low as 54% during 1-year follow-up have been suggested.[34] Therefore, our results being viewed in light of previous large-scale epidemiologic studies allow for meaningful conclusions to be drawn even if we did not include a control group.

In conclusion, PRP is an effective adjunct to enhance would healing and increase limb salvage in diabetic patients with concomitant PAD. Limb loss is significantly higher in diabetic patients presenting with CLI compared with those without and therefore revascularization should be attempted in the former group. Nevertheless, GFs may be used even in patients with CLI to assist treatment of foot ulceration.

Declaration of Conflicting Interests

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CLINICAL INVESTIGATION

Direct Stenting in Patients with Acute Lower Limb Arterial Occlusions: Immediate and Long-Term Results

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Abstract
Purpose The purpose of this study is to accentuate the efficacy of direct stenting (stent placement without predilatation of the lesion) in patients with acute lower limb arterial ischemia (ALLI).
Materials and Methods Between January 2010 and September 2015, 16 patients (11 men and 5 women) underwent direct stenting of acute arterial occlusions. All patients had contraindication for surgical revascularization or catheter-directed thrombolysis. According to SVS/ISCVS Classification, six patients had IIa and ten patients IIb ALLI. The occlusions were located in CIA, EIA, SFA, or popliteal artery. Mean follow-up time with clinical examination and color Duplex ultrasonography was 37.6 months (range 1–72). We analyzed the technical and clinical outcomes of the procedures, as well the complications and patency rates.
Results Technical success was achieved in all patients (16/16) and there was significant clinical improvement in 15 patients. There was neither distal embolization nor procedure-related complications. During the 6 years of follow-up, four patients died due to non-procedure-related causes and there were two minor and one major amputations. The primary patency rates and the amputation-free survival rates were 93.7 and 87% at 1 year, 75.2 and 71.2% at 3 years, and 75.2 and 62.3%, respectively, at 6 years.
Conclusions Direct stenting may be a valuable alternative procedure for acute arterial occlusions in selected cases with high technical success and significant clinical improvement.
Level of Evidence Level 4, Case Series.

Keywords Acute Limb Ischemia · Direct stenting · Embolism · Thrombosis · Iliac artery · Superficial femoral artery · Popliteal artery · Recanalization · Nitinol stent · Vascular intervention

Introduction

Acute lower limb ischemia (ALLI) represents a quickly developing or sudden decrease in limb perfusion, resulting in a potential threat to the viability of the extremity [1]. The hypoperfusion also impairs cardiopulmonary and renal function due to systemic acid–base and electrolyte abnormalities [2]. Causes of ALLI include acute thrombosis of a limb artery or bypass graft, embolism from the heart, dissection, and trauma [3]. A limb-threatening ischemic event is characterized acute if the duration of symptoms is less than 14 days, subacute between 15 days and 3 months, and chronic after 3 months [4]. A patient with ALLI often presents with the "5 P's" of paresthesia, pain, pallor, pulselessness, and paralysis, and the incidence is about 1.5 cases per 10,000 persons per year [5]. Patients with ALLI have poor short-term outcomes, with a risk of amputation between 10 and 30% and a mortality rate of approximately 15–20% in the first year, mainly in the peri-operative period [1, 6].

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The management includes either surgical procedures [7–10] or percutaneous endovascular procedures such us catheter-directed thrombolysis, manual aspiration thrombectomy, and mechanical thrombectomy [4, 11–14]. Surgical revascularization is the classic treatment and includes procedures such us embolectomy with a Fogarty catheter, bypass grafting, and endarterectomy [3]. Despite there is no significant difference in limb salvage rate or mortality between surgical procedures and catheter-directed thrombolysis [8], surgical procedures are associated with higher incidence of infections, rethrombosis, or fasciotomy [10]. Surgical procedures and administration of anesthesia are associated with a complex stress response. The American Society of Anesthesiologists (ASA) grading system offers a simple description of the physical state of a patient and is a component of the overall procedural risk [15]. Despite improvements in pre- and peri-operative management, arterial thromboembolectomy is characterized by high morbidity and mortality in elderly patients with an ASA score $\geq$ III [16]. On the other hand, catheter-directed thrombolysis may be effective for treating acute limb ischemia caused by thrombotic or embolic occlusions but it is associated with substantial risk of major hemorrhage and stroke [9, 17, 18]. There are also absolute or relative contraindications for catheter-directed thrombolysis such us ongoing bleeding, intracranial hemorrhage, compartment syndrome, recent eye surgery, and recent gastrointestinal bleeding. Moreover it cannot be used in patients with severe limb ischemia that require immediate recanalization due to the longer procedural time [14]. Percutaneous aspiration thrombectomy and percutaneous mechanical thrombectomy are efficient methods for transluminal removal of thrombus but they are associated with high risk for distal embolization (up to 28%), and they also require larger sheaths, which can lead to puncture-site complications (hematoma, dissection) [12].

Reperfusion injury is a common complication after revascularization which can lead to rapid development of compartment syndrome. In this case, surgical fasciotomy is necessary to prevent irreversible neurologic and muscular damage [3]. ALLI despite recent advancements in treatment strategies continues to confer significant risks for patients' limb and life, and since currently available surgical or endovascular strategies are not without adverse events and contraindications, there is an obvious necessity for new techniques to be developed.

In this study, we present long-term results in patients with acute arterial occlusions who were treated with direct stenting (stent placement without predilatation of the lesion).

Materials and Methods

Study Design and Patient Selection

This is an observational, retrospective, single-center study aiming to examine efficacy of direct stenting to treat patients presenting with ALLI. Approval was obtained from our institutional review board to conduct this retrospective study. According to local treatment protocols and in accordance to international guidelines, patients presenting with SVS/ISCVS III ALLI (irreversible ischemia) were subjected to primary amputation. Those with SVS/ISCVS I, IIa, and IIb (viable, marginally, and immediately threatened limbs, respectively) were initially subjected to computed tomography (CT) imaging, and the subsequent management was determined on a consensus between vascular surgeons and interventional radiologists. 24-hour availability of the interventional radiology unit allowed for the alternative of the endovascular treatment to be available even for patients with immediately threatened limbs. Patients were allocated to treatment with direct stenting technique according to the following selection criteria:

1. Compromised patients with ASA score class III or IV who are not ideal candidates for surgery
2. Native artery occlusion (ALLI due to graft thrombosis excluded)
3. Contraindication for administration of thrombolytic agents
4. At least one tibial vessel runoff in the CTA

Patient Data: Clinical Information (Table 1)

From January 2010 to September 2015, 120 patients were diagnosed with ALLI at our institution. Among those, 16 patients (11 men and 5 women), aged between 52 and 93 years (median age 72.5 years), underwent direct stenting of acute arterial occlusions. In all patients, the duration of symptoms was less than 2 weeks with a mean duration of 2 days. Categorized in SVS/ISCVS Classification of ALLI, six patients were allocated to class IIa with minimal sensory deficit but no motor deficit and ten patients were allocated to class IIb with sensory deficit and mild to moderate motor deficit. Arterial doppler signal at the level of the malleolus was not detected in the affected limbs of all patients. The affected limbs could be salvageable if immediate revascularization took place.

The main risk factors were hypertension ($n = 10$), hyperlipidemia ($n = 8$), diabetes mellitus ($n = 9$), atrial fibrillation ($n = 4$), smoking ($n = 6$), previous acute myocardial infarction or ischemic stroke ($n = 4$), and previous endovascular or surgical procedure ($n = 5$).

Table 1 Clinical data of patients with ALLI

Pt no.	Sex	Age	Risk factors for ALLI	SVS/ISCVS classification	Lesion location	Lesion length (mm)	Duration of symptoms (days)	Contraindications to percutaneous catheter-directed thrombolysis
1	M	63	HT, DM, HL	IIb	(R) SFA	80	2	Severe limb ischemia
2	F	83	HT	IIa	(R) SFA	60	1	Recent eye surgery
3	M	57	HT, HL	IIb	(L) CIA	60	1	Severe limb ischemia
4	M	78	HT, DM, HL, AS	IIb	(L) POPA	100	2	Recent hemorrhagic stroke
5	M	79	DM, HL, AS, AMI	IIb	(R) SFA	120	2	Severe limb ischemia
6	M	55	HL	IIa	(L) EIA	40	6	Severe limb ischemia
7	M	87	HT, SM, CRF	IIb	(R) SFA, (R) POPA	130	3	Severe limb ischemia
8	F	93	DM, HL	IIb	(R) EIA	100	2	Severe limb ischemia
9	M	55	DM, SM	IIb	(R) SFA	40	1	Severe limb ischemia
10	M	52	HT, DM, SM, AMI	IIa	(L) CIA, (L) EIA	100	1	Intracranial trauma 2 months ago
11	F	80	HT, DM, HL, AF	IIa	(L) CIA, (L) EIA	160	1	Diabetic hemorrhagic retinopathy
12	M	79	HT, SM	IIa	(L) CIA	60	4	Severe limb ischemia
13	F	67	DM, AF	IIb	(R) CIA, (R)EIA	80	2	Severe limb ischemia
14	M	66	HL, SM, AF	IIb	(L) EIA, (R) EIA	(L) 80 (R) 100	1	Severe limb ischemia
15	F	61	HT, SM	IIa	(R) SFA (R) POPA	60	1	Recent gastrointestinal bleeding
16	M	90	HT, DM, AF	IIb	(R) POPA	50	2	Severe limb ischemia

M male, *F* female, *HT* hypertension, *DM* diabetes mellitus, *HL* hyperlipidemia, *SM* smoking, *AF* atrial fibrillation, *AMI* acute myocardial infarction, *AS* acute stroke, *CRF* chronic renal failure, *CIA* common iliac artery, *EIA* external iliac artery, *SFA* superficial femoral artery, *POPA* popliteal artery

All patients underwent lower extremity CT angiography (CTA) which revealed occlusions in CIA ($n = 5$), EIA ($n = 7$), SFA ($n = 6$), or POPA ($n = 4$) taking into consideration that some patients had more than one occlusion. In 12 patients, the cause of ALLI was assumed acute in situ thrombosis in a pre-existing atherosclerotic occlusion while in four patients embolism from the heart. The patients were considered as high risk for surgery due to multiple comorbidities so they were transferred to the interventional radiology suite for endovascular recanalization. Catheter-directed thrombolysis was not considered as a treatment option either because it was contraindicated (history of previous intracranial hemorrhage, recent eye surgery, recent intracranial trauma, diabetic hemorrhagic retinopathy, recent gastrointestinal bleeding) or the severity of limb ischemic symptoms was such that prompted immediate revascularization. Availability of percutaneous mechanical thrombectomy catheters is intermittent in our institute, and there was lack of these devices during treatment of the patients included in our study.

Procedural Details

Percutaneous common femoral arterial access was performed under real time U/S guidance. Depending on ipsilateral antegrade or contralateral retrograde approach, 5–6F vascular sheaths of variable lengths were inserted with their tip close to the occluded segment.

Our typical treatment strategy is to initially attempt crossing the occluded segment intraluminally using a 0.035 in. straight or curved hydrophilic guide wire (Terumo, Japan) supported by a standard 5F straight or curved catheter. In all patients, the occlusions were easily traversed intraluminally with straight type hydrophilic guide wires, a sign strongly predicting the presence of soft thrombus. Subsequently, self-expanding nitinol stents (Complete, Medtronic), (Luminexx, Bard), (Maris, Medtronic), (Sinus-SuperFlex, OptiMed), (Zeus SX, Rontis Medical) (Protege Everflex, Covidien) were deployed across the lesions. The selection of the self-expanding nitinol stent was based on the availability of the desired stent (diameter and length) in our department at that time.

Deployment of a single long stent was preferred over implantation of multiple overlapping stents. Routinely, self-expanding nitinol stents should be 1–2 mm greater than the artery diameter. In our cases, the stent diameter was selected to be similar to the vessel diameter as it was measured before and after the occluded segment to prevent clot prolapse. As far as the stent length, it was about 20 mm longer than the lesion (10 mm proximal and 10 mm distal to the occlusion) to avoid thrombus relocation through both stent ends. Post-dilatation was performed only if there was more than 30% residual stenosis using slightly undersized angioplasty balloons at low pressures to avoid laceration and dislodgement of thrombus which could cause distal embolization. Apart from that the thermal memory of self-expanding nitinol stents would allow them to expand at the beneficial size.

The patients received a bolus of 5000 IU of heparin intra-arterially during the procedure. After the endovascular procedure, anticoagulant and antiplatelet therapy was important not only to obtain patency but to prevent recurrence. Patients with emboli of cardiac origin were placed on long-term anticoagulation with warfarin (INR: 2–3). Patients with non-embolic local arterial thrombosis received dual antiplatelet therapy including clopidogrel (75 mg once daily) and aspirin (100 mg once daily) for 1 month and then aspirin (100 mg once daily) indefinitely.

Endpoints

Primary endpoints of the analysis were efficacy measures of 30-day and long-term survival as well as 30-day and long-term limb salvage rate. Secondary outcomes that were assessed included procedural details like technical success, contrast administration, as well as safety measures like complication rate and distal embolization during the procedure. Reperfusion injury and need for fasciotomy were recorded. Patients were followed up with clinical examination at 1, 3, 6, and 12 months and color Doppler ultrasound combined with clinical examination on an annual basis. Patency and reintervention rates were also calculated.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). Amputation-free survival and overall survival were evaluated using Kaplan–Meier statistics. Amputation-free survival is a composite metric which incorporates the hard endpoints of mortality and major amputation. Toe and distal foot amputations were considered minor amputations.

Results

Procedural Details: Outcome Measures (Table 2)

Recanalization was technically successful in all patients. There were no significant residual stenoses in the stented segments and there was neither distal embolization nor acute in-stent thrombosis, as it confirmed with the final angiography (Figs. 1, 2). There were no complications related to femoral arterial catheterizations such as hematomas, pseudoaneurysms, or arteriovenous fistulas. In 15 of 16 patients, there was a significant clinical improvement with immediate relief of symptoms. After the procedure, 14/16 patients restored palpable pedal pulses, while median post-procedural ABI was 0.8 (range 0.2–1.1). During the first week after the procedure, there was one case of in-stent thrombosis followed by above-knee amputation. The patients were followed up with clinical examination and color Duplex ultrasonography for a mean duration period of 37.6 months (SD 24.9 months, range 1–72). During follow-up, four patients died due to non-procedure-related causes (colon cancer, breast cancer, myocardial infarction, ischemic stroke) and there were two minor (toe) amputations and one major (above-knee) amputation. The amputations took place during the first year after the procedure. The 1-, 3- and 6-year survival rates, estimated by Kaplan–Meier analysis, were 93.3% [95% confidence interval (CI) 61.2–99%], 77.8% (95% CI 45.5–92.3%), and 69.1% (95% CI 36.7–87.3%), respectively, and the 1-, 3- and 6-year Amputation-free survival rates were 87% (95% CI 57.3–96.6%), 71.2% (95% CI 39.8–88.2%), and 62.3% (95% CI 31–82.6%), respectively (Fig. 3). The primary patency rate (defined as exempt from in-stent-restenosis greater than 50%) was 93.7% (95% CI 63.2–99.1%) at 1 year, 85.9% (95% CI 54–96.3%) at 2 years, and 75.2% (95% CI 39.4–91.6%) at 3 to 6 years (Fig. 4). No reperfusion injury was observed in this series and fasciotomy was not necessary in any of the patients treated.

Discussion

Acute limb ischemia is a sudden decrease in limb perfusion that threatens the viability of the extremity and requires immediate revascularization.

Stenting has been used successfully in acute myocardial infarction after failed thrombolysis [19] or after unsuccessful emergency angioplasty [20] but is also an effective primary revascularization strategy with many advantages compared with PTCA [21]. Primary intracranial stenting is also a safe and feasible approach for patients with acute ischemic stroke [22, 23]. Moreover, primary or direct

Table 2 Procedural details and clinical outcome of patients with ALLI

Pt no.	Technical success	Clinical success	Number of stents used	Type of stent	Post-dilatation	Distal embolization/ reperfusion injury	Duration of follow-up with clinical examination and color duplex U/S (months)	Amputation	Cause of death	In-stent stenosis >50%
1	Yes	Yes	2	LUMINEX 7 × 60 mm, LUMINEX 7 × 40 mm	Yes	No	72	Toe amputation 2 months later	Alive	No
2	Yes	Yes	1	COMPLETE 5 × 80 mm	Yes	No	72	No	Alive	No
3	Yes	Yes	1	LUMINEX 10 × 80 mm	No	No	72	No	Alive	No
4	Yes	Yes	1	COMPLETE 6 × 120 mm	Yes	No	1	Toe amputation 1 month later	AMI 12 months later	No
5	Yes	No	1	COMPLETE 6 × 150 mm	Yes	No	6	Above-knee amputation 1 week later	Alive	In-stent thrombosis 1 week later
6	Yes	Yes	1	LUMINEX 8 × 60 mm	No	No	60	No	Alive	No
7	Yes	Yes	1	COMPLETE 7 × 150 mm	Yes	No	24	No	Colon cancer 27 months later	No
8	Yes	Yes	1	MARIS 6 × 120 mm	No	No	24	No	Breast cancer 33 months later	No
9	Yes	Yes	1	ZEUS SX 6 × 60 mm	No	No	36	No	AIS 40 months later	At proximal edge 2 years later
10	Yes	Yes	1	MARIS 6 × 120 mm	No	No	60	No	Alive	No
11	Yes	Yes	1	SINUS-SUPERFLEX 7 × 200 mm	No	No	48	No	Alive	No
12	Yes	Yes	1	SINUS-SUPERFLEX 9 × 80 mm	Yes	No	48	No	Alive	At proximal edge 3 years later
13	Yes	Yes	1	ZEUS SX 8 × 100 mm	No	No	36	No	Alive	No
14	Yes	Yes	2	PROTEGE EVERFLEX 7 × 100 mm, 7 × 120 mm	Yes	No	24	No	Alive	No
15	Yes	Yes	1	PROTEGE EVERFLEX 5 × 80 mm	Yes	No	12	No	Alive	No
16	Yes	Yes	1	PROTEGE EVERFLEX 6 × 60 mm	Yes	No	6	No	Alive	No

AIS acute ischemic stroke, *AMI* acute myocardial infarction

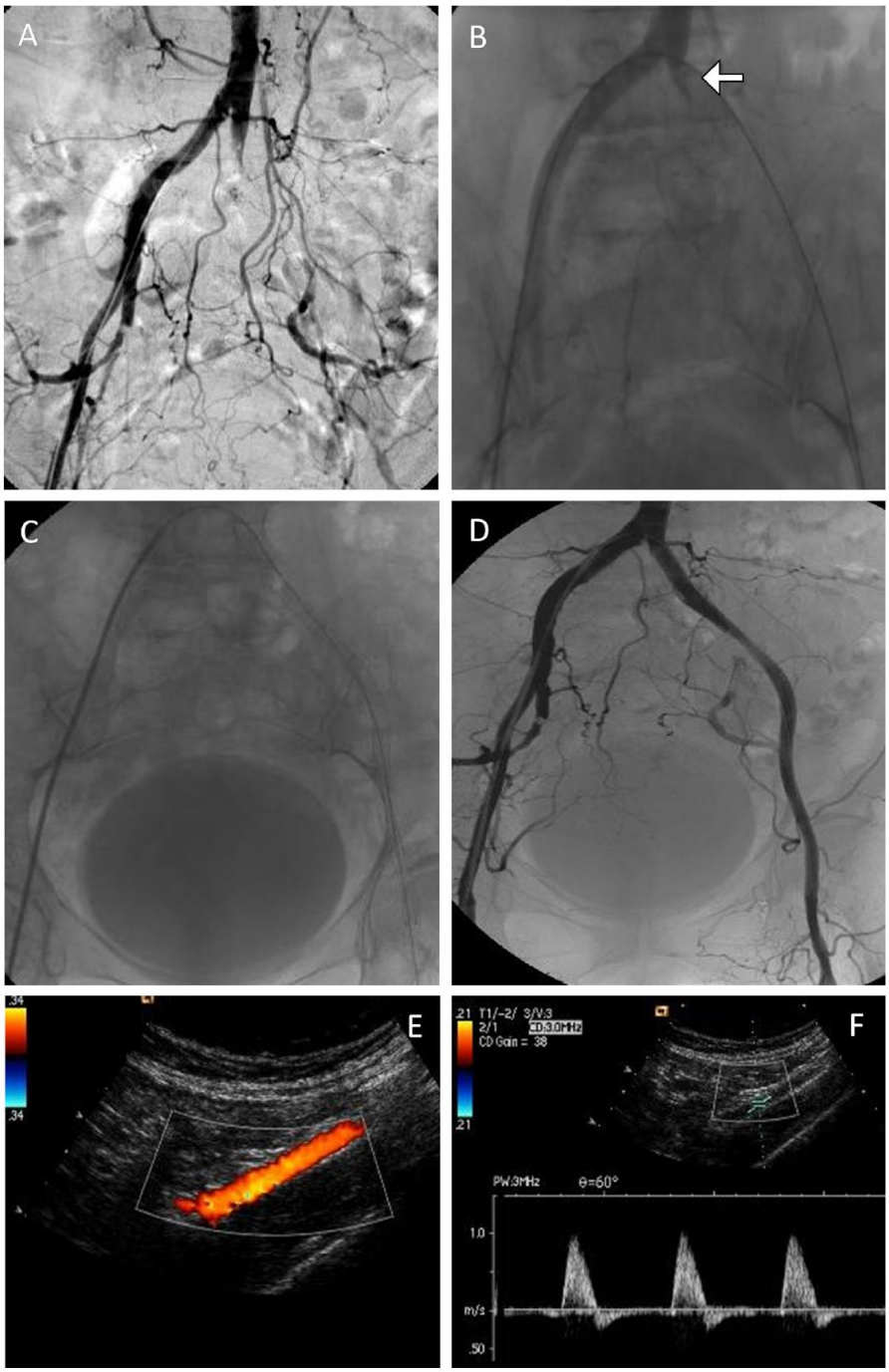

Fig. 1 A 80-year-old patient with atrial fibrillation. **A** DSA showed total occlusion of left CIA and left EIA. **B** Through percutaneous crossover approach from the right common femoral artery, the acute occlusion was traversed with a hydrophilic guide wire. Note the left CIA filling defect in the proximal end of the occlusion (*arrow*), typical for acute thrombus. **C** A self-expanding 7 × 200 mm nitinol stent was deployed across the lesion and **D** flow restoration was immediately achieved without distal embolization or other complications. **E**, **F** 4 years later the patient was asymptomatic. On color Duplex follow-up, the stented segment and distal runoff arteries remained patent with no significant restenosis

stenting is an acceptable revascularization treatment for peripheral artery disease [1]. It is effective both for iliac artery occlusive disease [24] and femoropopliteal disease [25]. Direct stenting is not considered as a standard treatment option for ALLI due to a risk of distal embolization, which worsens the ischemia. So far there are only a few reports of patients with ALLI treated with stenting. Yilmaz et al. treated six patients with embolic occlusions in the common or external iliac arteries with primary stenting without complications [26]. Berczi et al. reported seven patients with acute thrombotic occlusions in the iliac arteries, who underwent stent implantation with no

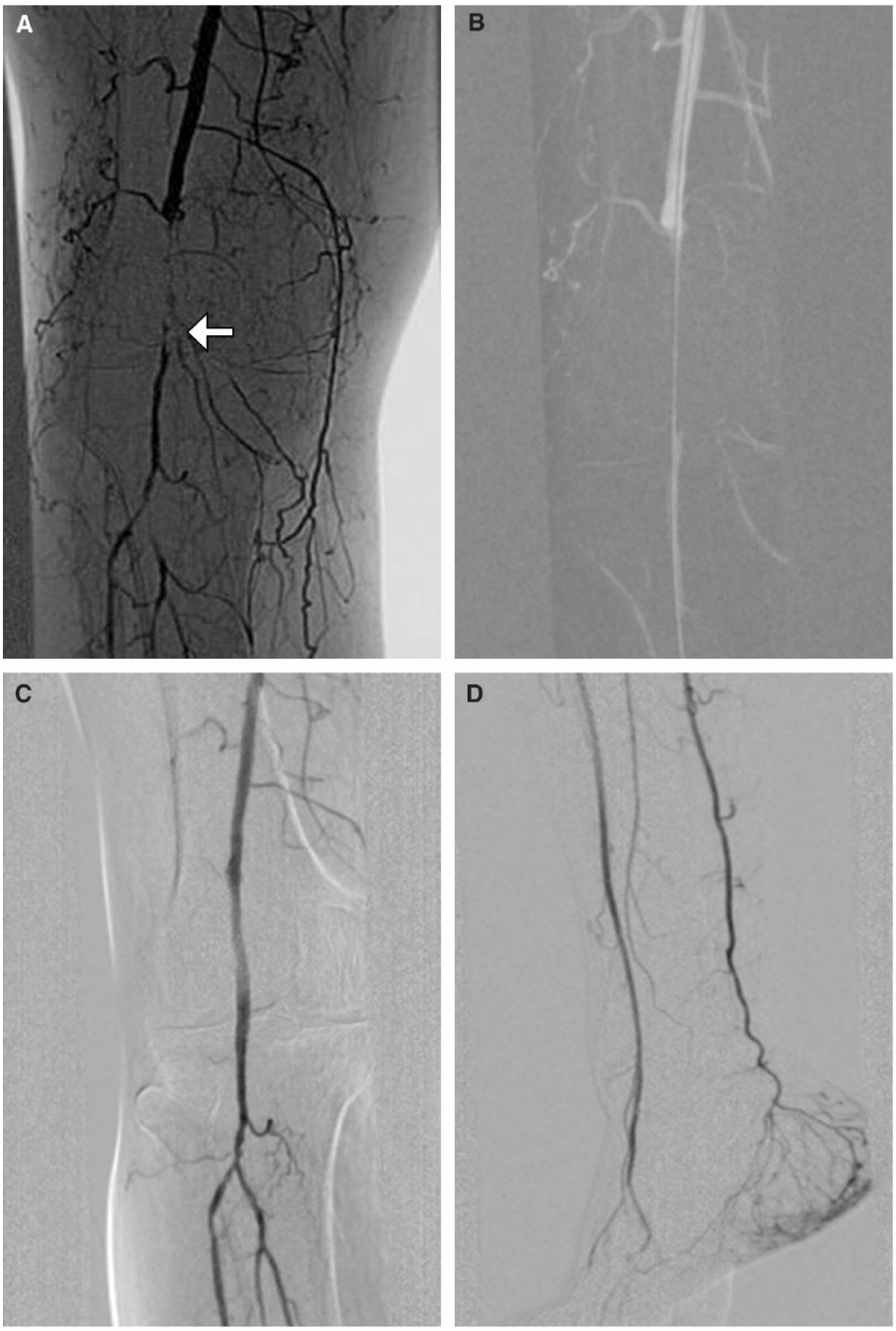

Fig. 2 A 91-year-old patient with right acute lower limb ischemia. **A** DSA showed a thrombotic occlusion of the right popliteal artery with a small intraluminal filling defect in the distal end of the occlusion (*arrow*) consistent with the presence of fresh thrombus. **B** The occlusion was intraluminally traversed with a hydrophilic guide wire. **C** Following the implantation of a 6 × 60 mm self-expanding nitinol stent, DSA demonstrated significant flow restoration. **D** Conclusion DSA showed no evidence of distal embolization in the distal runoff arteries

significant embolic complications [27]. Raja et al. reviewed 4 patients with acute thrombotic or embolic occlusions in iliac or femoropopliteal arteries who were treated with stenting [28]. Finally Kim et al. treated fifteen patients with ALLI with stent implantation with significant technical and clinical success [29].

Our study includes the largest number of patients with ALLI, treated with primary or direct stenting ($n = 16$) and the longest follow-up (mean duration of about 3 years), which confirms a sustainable clinical improvement and low risk for amputation. In our study, we applied direct stenting as a primary endovascular treatment due to unavailability of percutaneous mechanical thrombectomy catheters at the time of cases presentation, while catheter-directed thrombolysis was either contraindicated or was considered too time consuming for immediate limb revascularization. Our

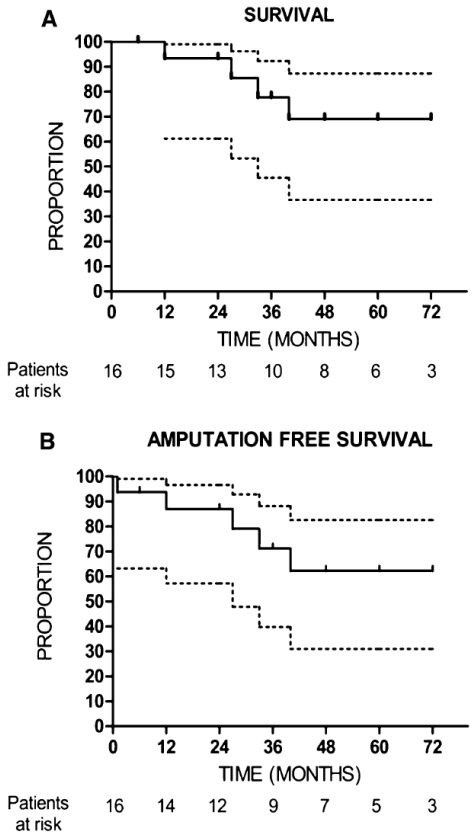

Fig. 3 The survival curves (±95% confidence interval) were calculated by Kaplan–Meier method. The *x*-axis shows months of follow-up, the *y*-axis shows proportion of patients remaining alive (**A**) or alive without major amputation (**B**). The number of patients at risk is indicated for each time point during follow-up

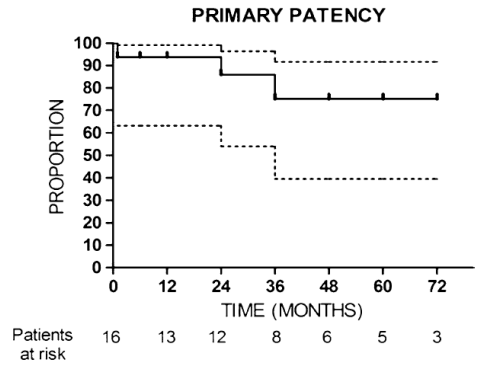

Fig. 4 Kaplan–Meier curve of primary patency (±95% confidence interval) after stent placement. The number of patients at risk for each follow-up period is also indicated

findings indicate that direct stenting is an attractive therapeutic alternative for the management of patients with ALLI whenever feasible. The 100% technical success rate recorded in our study cohort compares favorably with the results of other reports employing the traditional and widely accepted techniques of catheter-directed thrombolysis and percutaneous mechanical thrombectomy. Furthermore, we neither encountered puncture-site complications nor distal embolization which confirms the safety of this technique in patients with ALLI. From our clinical experience, immediate recanalization of acute arterial occlusions with direct stenting did not induce compartment syndrome or systemic inflammatory response triggered by reperfusion injury in any patients at least to an extent that needed any further concomitant treatment. We used only self-expanding nitinol stents to avoid laceration and dislodgement of thrombus and reduce the traumatic injury of the vessel. Drug-eluting stents (DES) improve patency rates and reduce the risk of reintervention compared with PTA or bare-metal stents (BMS) in atherosclerotic disease of femoral, popliteal [30], and infrapopliteal arteries [31]. However, there are no reported cases of the use of DES in ALLI. Stents in the femoropopliteal system and especially if the lesions expanded in the inguinal ligament or knee joint have historically been associated with increased rate of stent fracture and restenosis. Modern self-expanding nitinol stents with their resistance to external deformation and their thermal memory properties are sometimes indicated for placement in areas of flexion (close to the inguinal ligament, in the adductor canal and at the knee joint) [32]. Multiple studies have reported the use of flexible self-expanding nitinol stents in the popliteal artery and lesions which were extended into the below-knee segment with good patency rates [33]. In our study, we avoided stent placement when the lesion crossing joints and there was only one patient (Fig. 2) who underwent direct stenting of popliteal artery occlusion crossing the knee joint. This patient was 90-year-old, presenting multiple comorbidities and was partially immobilized for 2 years. Therefore, he was a poor surgical candidate presenting also contraindication for catheter-directed thrombolysis. In this instance, direct stenting seemed an appealing therapeutic option even if the stent would be crossing the knee joint. Despite the fact that the lesions observed in this series were relatively long, technical success was achieved in all patients. Other authors who performed direct stenting for ALLI encountered similar long arterial occlusions (up to 150 mm) [26–29]. All stents deployed in the studied patients were commercially available self-expanding nitinol ones with different strut configuration and it would be interesting to analyze in

larger cohort studies the potential influence of strut design to overall nitinol stent performance in the ALLI setting.

In conclusion, direct stenting appears to be a safe, effective, and durable treatment for patients with ALLI who require immediate recanalization and they have contraindications for catheter-directed thrombolysis or surgical revascularization.

Compliance of Ethical Standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Incidence and Endovascular Treatment of Isolated Atherosclerotic Popliteal Artery Disease: Outcomes from the IPAD Multicenter Study

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Abstract

Purpose To report the incidence and long-term outcomes following endovascular treatment of symptomatic, atherosclerotic isolated popliteal artery disease (IPAD).

Materials and Methods This retrospective, multicenter study included all patients who underwent endovascular treatment of IPAD between January 2010 and December 2016 because of intermittent claudication or critical limb ischemia (CLI), in three tertiary University Hospitals. In total, 4717 peripheral arterial disease (PAD) procedures were analyzed. The study's primary outcome measures were: IPAD incidence, binary restenosis rate and freedom from target lesion revascularization (TLR). Secondary outcome measures included technical success, limb salvage rate and the identification of predictors of outcomes.

Results The incidence of IPAD was 0.98% (46/4717 PAD procedures). In total, 46 patients (38 male; mean age 73 ± 12 years) underwent plain balloon (69.5%) or bail-out stenting (30.5%) procedures. Most patients suffered from CLI (65.2%). Mean lesion length was 52.5 ± 32.0 mm and 45.6% of the cases were occlusions. Severe calcifications were noted in 26.1%. Technical success was 100%. Mean time follow-up was 32.6 ± 25.6 months. According to Kaplan–Meier analysis, restenosis was 15.8, 40.9, 45.8% and TLR-free rate was 90.5, 79.0, 74.1%, at 1, 2 and 3 years, respectively. Survival and limb salvage rates were 73.6 and 88.1%, at

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5 years, respectively. The major amputation rate for CLI patients was 10.0% (3/29 limbs), while no major amputations occurred in the claudication subgroup. Cox multivariable analysis detected baseline occlusion as an independent predictor of increased restenosis (HR 5.3; 95% CI 0.21–0.66, $p = 0.02$).
Conclusions Isolated popliteal lesions requiring treatment appear in nearly 1% of patients with PAD. Balloon angioplasty and bail-out stenting resulted in acceptable long-term clinical outcomes. Treatment of occlusions was correlated with increased restenosis rate.

Keywords Isolated popliteal lesions · Atherosclerosis · Popliteal stenosis · Popliteal occlusion · Intermittent claudication · Critical limb ischemia · Angioplasty · Stent

Introduction

Minimal invasive, percutaneous, endovascular treatment is continuously gaining ground as a first-line treatment of intermittent claudication (IC) or critical limb ischemia (CLI). This is mainly due to the increasing experience and the improvement of endovascular devices, both resulting in constantly increasing technical success and lower complication rates, even in complex peripheral arterial disease (PAD) cases [1, 2]. One of the most challenging anatomical locations for endovascular treatment of atherosclerotic disease has always been the popliteal artery [3]. The specific anatomical location and unique biomechanical attributes of the popliteal artery result in low mid-term patency rates following plain balloon angioplasty, while stenting has been traditionally reserved for bail-out cases due to the increased risk of stent deformation or fracture which has been related to decreased patency [4]. Moreover, a recent multicenter, randomized controlled trial (RCT), investigating stenting versus plain balloon angioplasty for popliteal artery treatment demonstrated comparable 2-year patency rates following either provisional or primary stenting [5].

Although endovascular treatment options to improve immediate technical success and long-term patency of femoropopliteal atherosclerotic arterial disease has been widely investigated in several, large-scale, multicenter RCTs, data regarding the performance of angioplasty and bail-out stenting in isolated atherosclerotic popliteal artery disease (IPAD) remain limited to one multicenter RCT and few single-center, retrospective analyses, while long-term data, beyond 2 years, do not exist [5–10].

The aim of this multicenter study was to investigate the incidence and long-term outcomes of angioplasty and bail-out stenting for the treatment of IPAD performed in the Interventional Radiology Departments of three large, tertiary University Hospitals.

Materials and Methods

This retrospective, multicenter, single-arm study included all patients undergoing endovascular treatment of IPAD between January 2010 and December 2016 because of intermittent claudication or critical limb ischemia (CLI), in three tertiary Hospitals. In total, 4717 peripheral arterial disease procedures were performed within the study period. The patients' medical and imaging records were scrutinized. Inclusion criteria were: age $\geq$ 18 years old, Rutherford–Becker classification between 2 and 5, de novo $\geq$ 50% angiographic stenosis or occlusion in the PA according to visual estimation and treatment with plain balloon angioplasty and/or bare metal stenting. The PA was radiographically divided into three segments as follows: P1 (between the arterial intersection with the femoral bone and the upper edge of the patella), P2 (between the upper limit of the patella and the superior surface of the tibial condyle) and P3 (between the superior surface of the tibial condyle and the infrapopliteal arterial bifurcation of the anterior tibial artery and the tibioperoneal trunk). Exclusion criteria were: lesions requiring intervention (endovascular or surgical) involving the proximal inflow (aorta, iliac arteries, common femoral artery, SFA) or the arterial outflow (infrapopliteal arteries), and standard angioplasty contraindications (pregnancy, uncorrectable coagulopathy, impaired renal status and history of severe, life-threatening allergy to contrast).

The decision to proceed with endovascular rather than surgical treatment was discussed at the multidisciplinary team meeting between vascular surgeons and interventional radiologists and was case-sensitive. In general, endovascular revascularization was decided for patients at high-surgical risk or those with stenosis or short occlusions. Procedures were performed using standard endovascular techniques [5, 8]. In brief, all patients were prescribed antiplatelet therapy (monotherapy with aspirin 100 mg or clopidogrel 75 mg once daily or dual therapy with aspirin 100 mg and clopidogrel 75 mg once daily according to the physicians' preference) at least 5 days prior to the procedure. Following the placement of an arterial sheath, a bolus dose of 5000 IU of heparin was administered. Intraluminal or subintimal lesion crossing was performed, using standard guide wires and catheters. Balloon angioplasty was the initial treatment of choice, and bail-out stenting was used in cases of suboptimal

angioplasty result (> 30% remaining stenosis by visual estimation and flow-limiting type C dissection). Hemostasis was achieved by either manual compression or arterial closure devices. After the procedure, antiplatelet therapy regiment and duration was administrated on a case basis and according to the physicians' preference. In general, dual antiplatelet therapy with clopidogrel 75 mg and aspirin 100 mg once daily was administrated for at least one month and up to 6 months, following the procedure and single antiplatelet therapy with either clopidogrel 75 mg or aspirin 100 mg once daily was then continued for life. Procedural details are reported in Table 1.

Definitions Endpoints and Follow-up

The study's primary outcome measures were: (1) IPAD incidence defined as the proportion of patients receiving endovascular treatment for IPAD within the population of patients who received endovascular treatment for PAD during the 7-year study period. (2) Binary restenosis defined as ≥ 50% restenosis of the target lesion according to duplex ultrasound (DUS; peak systolic velocity ratio > 2.4) or digital subtracted angiography (DSA; performed in cases of re-intervention) and (3) freedom from clinically driven (symptoms relapse) target lesion revascularization (TLR) due to angiographically verified (intraprocedural) target lesion restenosis. Secondary outcome measures were technical success defined as residual target lesion stenosis of < 30% (by visual estimation) without type C (flow limiting) target vessel dissection at completion DSA following balloon angioplasty or stenting, limb salvage (i.e., amputation above the level of the ankle), and complications defined as major or minor according to international guidelines [11], as well as the identification of independent predictors of outcomes. Severe calcifications of the lesion were defined as radiopacities on both sides of the arterial wall and extending > 1 cm of length at plain fluoroscopy. Mild calcifications were defined as calcifications noted without fulfilling all previous criteria.

Follow-up visits were scheduled at 6 and 12 months and yearly thereafter (unless a non-scheduled visit was required due to relapse) and included clinical examination, Rutherford–Becker classification of the disease and target lesion evaluation by DUS.

Table 1 Patient demographics

Variable	*N* (%)
Patients	46
Limbs	46
Male	32 (82.6)
Age; mean ± SD (range)	73 ± 12 (48–90)
Cardiac disease	21 (45.6)
Diabetes mellitus	35 (76.1)
Renal disease	11 (23.9)
Hyperlipidemia	31 (67.4)
Smoking habit	13 (28.2)
Hypertension	35 (76.1)
Stroke/TIA	8 (17.4)
Rutherford–Becker classification	
3	16 (34.8)
4	11 (23.9)
5	18 (39.1)
6	1 (2.2)

Continuous data are presented as mean ± SE; categorical data are given as counts and percentages (parentheses)

Statistical Analysis

Discrete variables are reported as counts and percentages, while continuous variables as medians and interquartile ranges (i.e., between the 25th and 75th percentiles) in parentheses or as mean ± standard error (SE) if they passed the normality test as stated below. The Kaplan–Meier analysis method was employed for calculation of the cumulative proportion outcomes of restenosis, TLR-free, survival and limb salvage rates. Exploratory univariate subgroup analysis for primary and secondary outcome measures was performed using the following dependent variables: baseline symptoms (critical limb ischemia or intermittent claudication), diabetes mellitus, increased serum creatinine level (> 1.5 mg/dL), nicotine use (up to the preceding 12 months), cardiac disease (coronary disease, cardiac insufficiency, severe arrhythmia), hyperlipidemia (controlled with diet or drugs), initial lesion grade (stenosis or occlusion), TASC II lesion classification, runoff vessels (1–3), severe calcifications of the lesion defined as radiopacities on both sides of the arterial wall and extending > 1 cm of length at plain fluoroscopy, popliteal segment (P1, P2, P3), subintimal or intraluminal lesion crossing and treatment modality (plain balloon angioplasty or stenting). Covariates with a p value < 0.15 according to an exploratory univariate analysis were included in the Cox multivariable stepwise regression analysis that was employed in order to identify independent risk factors affecting the study's outcome measures. Finally, the dependent variables assessed by the Cox multivariate stepwise regression analysis were stent deployment, cardiac disease, diabetes mellitus and baseline lesion grade. The results were expressed as hazard ratios with 95% confidence intervals (CIs) and the associated level of statistical significance, while the adjusted Cox curve plots of the identified covariate are presented only in cases of significant outcomes. Statistical analysis was

performed with the SPSS statistical software package (version 21.0; IBM, USA), with a threshold for statistical significance at a p value of 0.05.

Results

The incidence of IPAD was 0.98% (46/4717 peripheral arterial disease procedures). In total, 46 patients (38 male; 82.6%), with a mean age of 73 ± 12 years (range 48–90 years), underwent 32 plain balloon (69.5%) or 14 bail-out nitinol bare stent deployment (30.5%) procedures in 46 limbs. Stents used in this study were the S.M.A.R.T.® CONTROL® Self-Expanding Nitinol Stent (Cordis, Switzerland), the EVERFLEX™ Self-Expanding Peripheral Stent and the Complete® SE Vascular Stent System (Medtronic, USA) and the Zeus™ SX Nitinol Self-Expanding Stent System (Rontis Medical, Switzerland). Stent diameters were either 5 or 7 mm. Most patients suffered from CLI (30/46 cases; 65.2%), while 76.5% (35/46 cases) had diabetes, 32.9% (11/46 cases) were on dialysis and 28.2% (13/46) were active or recent smokers. Mean lesion length was 52.5 ± 32.0 mm (range 20–120 mm) with 45.6% of the lesions being occlusions (21/46 cases). In 15/46 cases (32.6%) the P2 segment and in 13/46 cases (28.3%) the infrapopliteal P3 segment were treated.

Technical success was 100% (46/46 cases). The subintimal technique was used in only 3/46 cases (6.5%). Severe calcifications were noted in 26.1% (12/46 cases) and mild calcifications in 15/46 cases (32.6%). Major complications did not occur. Minor complications included 6 small < 5 cm puncture-related groin hematomas (6/46; 13.0%). Patient demographics and procedural details are analytically reported in Table 1. Mean time follow-up was 32.6 ± 25.6 months (range 4–94 months).

According to Kaplan–Meier analysis, restenosis was 15.8, 40.9, 45.8% (numbers at risk: 27, 12, 9) and TLR-free interval was 90.5, 79.0, 74.1% (numbers at risk: 32, 20, 10), at 1, 2 and 3 years follow-up, respectively (Fig. 1). Patient survival rate was 97.5, 91.3 and 73.6% (numbers at risk: 40, 21, 9), and limb salvage was 95.4, 95.4 and 88.1% (numbers at risk: 39, 24, 12), at 1, 2 and 5-year follow-up; respectively (Fig. 1). The major amputation rate in the subgroup of patients suffering from CLI was 10.0% (3/29 limbs), while no major amputations occurred in the claudication subgroup. In total, 2/46 patients (4.3%) underwent bypass surgery due to lesion re-occlusion and symptoms relapse. The median (interquartile range) Rutherford class decreased from 4 (3–5) at baseline to 2 (1–2) at 1 month, 2 (1–3) at 12 months and 2 (2–3) at 5 years, respectively. A Rutherford classification improvement by at least 1-class compared to baseline was noted in 93.5% of the patients (43/46 cases) at one month, in 89.1% (41/46 cases) at 12 months and in 78.2% (36/46) at 5 years (Table 2).

Subgroup analysis of bail-out stenting versus plain balloon angioplasty demonstrated similar TLR-free (92.3 vs. 89.0%; $p = 0.13$, respectively at 1-year follow-up) and restenosis rates (84.6 vs. 80.0%; $p = 0.17$, at 1-year follow-up). According to Cox multivariable analysis, the only independent predictor of increased restenosis was baseline occlusion of the treated lesion (HR 5.3; 95% CI 0.21–0.66, $p = 0.02$) (Fig. 2).

Discussion

The importance of the herein presented results is that the incidence of IPAD was defined in a real-life multicenter clinical scenario, while the treatment strategy of plain balloon angioplasty with bail-out bare metal stenting resulted in acceptable outcomes up to 5-year follow-up. Specifically, the study involved three major tertiary, high volume, vascular centers, performing over 700 lower limb, chronic PAD, endovascular procedures per year. IPAD accounts for approximately 1% of lower limb endovascular revascularizations. Long-term restenosis and revascularization rates were low. Specifically, restenosis was nearly 50% at 3-year follow-up and consequently only 25% of the patients underwent re-intervention due to clinical relapse, during the same time period. These results are comparable to previously reported restenosis rates following IPAD treatment [4, 5]. Specifically, a recent multicenter RCT comparing stenting versus plain balloon angioplasty for IPAD, conducted by Rastan et al., reported similar 2-year restenosis rates of 35.8% in the stent group but higher for the PTA group (68.8%). Nevertheless, TLR rates were around 30% for both groups [5]. Interestingly, the reported restenosis rates following plain balloon angioplasty or stenting of the femoropopliteal arteries are significantly higher around 50–60% at 1 year [12–14]. One could speculate that IPAD cases demonstrate lower restenosis due to the short lesion length and the disease-free arterial inflow and outflow [15]. Lesion length and severe calcifications are two well-known independent predictors of decreased patency [16, 17]. In this study, almost half of the lesions were occlusions, and mean lesion length was short (approx 5 cm), while severe calcifications were noted only in 25% of the lesions. Interestingly, according to the multivariable analysis, baseline lesion occlusion was the only independent predictor of increased restenosis. Reduced patency following endovascular treatment of occlusions has been previously reported in the literature [18]. Nonetheless, other factors that have been usually correlated with worst outcomes such as diabetes, severe calcifications and lesion length were not verified in this

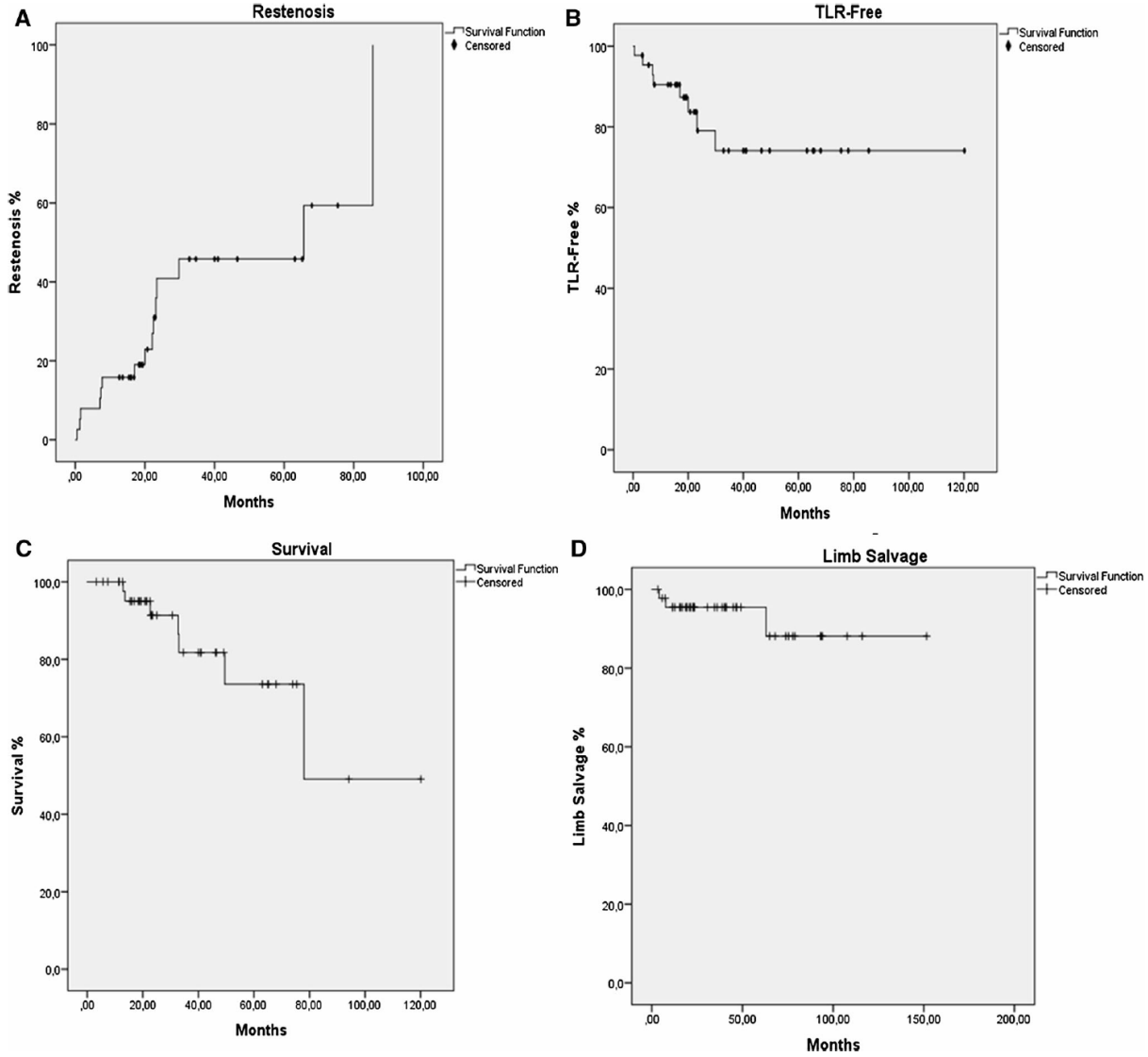

Fig. 1 Kaplan–Meier plots of **A** restenosis, **B** target lesion revascularization-free, **C** patient survival and **D** limb salvage rates

analysis [4, 15, 17]. This could be attributed to the small number of patients which certainly limited the validity of statistical analysis for these factors.

As for SFA lesions, primary stent deployment in the popliteal artery remains controversial [5, 17, 19]. According to subgroup analysis performed in this study, bail-out stenting achieved similar restenosis and re-intervention rates, while multivariable analysis indicated that stenting did not significantly improve outcomes. Stenting rate in this study (30.5%) was similar with previously published data investigating popliteal disease. Specifically, Chang et al. have reported a 35.6% stenting rate for popliteal lesions (18/52 cases) [4]. It could be discussed that stenting rate is high. Indeed, as this was a retrospective analysis without uniform predetermined criteria for bail-out stenting, cases of inappropriate bail-out stenting cannot be excluded. On the other hand, 45% of the lesions treated were chronic total occlusions and 26% were severely calcified, and thus a 30% stenting rate is probably justified. Bail-out nitinol stent deployment resulted in satisfactory outcomes aligned with previously reported data for IPAD endovascular treatment [5]. Following these results, the authors will continue to use nitinol stents as a bail-out option for IPAD. The use of novel interwoven stents, heparin-bonded stents or drug-eluting stents could further increase the patency of endovascular IPAD treatment [20]. On the other hand, in an area of high flexion such as the popliteal artery, drug-coated balloons, atherectomy devices

Table 2 Procedural details

Variable	*N* (%)
Lesions	46
Mean lesion length (mm)	52.5 ± 32.0
Popliteal segment treated	
P1	8 (17.4%)
P2	15 (32.6%)
P3	5 (10.8%)
P1–P2	10 (21.7%)
P2–P3	6 (13.0%)
P1–P2–P3	2 (4.3%)
Occlusions	21 (45.6%)
Calcifications	
None	19 (41.3%)
Mild	15 (32.6%)
Severe	12 (26.1)
Subintimal crossing	3 (6.5%)
Number of runoff vessels*	2 (2–3)
Sheath size	
4Fr	5 (10.8%)
6Fr	40 (86.9%)
7Fr	1 (2.3%)
Antegrade access	38 (82.6%)
Antiplatelet therapy	
Monotherapy	21 (45.6%)
Dual therapy	25 (54.4%)
Treatment type	
Balloon angioplasty	32 (69.5%)
Stent	14 (30.5%)

Continuous data are presented as mean ± SE; categorical data are given as counts and percentages (parentheses)

*Median value and interquartile range (IQR) in the parentheses

and their combination should be further investigated as these techniques could offer superior technical success rates with less dissection and recoil combined with superior patency rates without the use of metallic implants [21–23]. According to the authors' experience, a significant drawback of popliteal stenting is the increased difficulty of future endovascular revascularization in case of stent occlusion and a future surgical bypass inhibition. The 5-year limb salvage rate was 88% and overall, three major amputations occurred (6.5%) all in CLI patients with Rutherford–Becker class 5 disease. The major amputation rate in the CLI subgroup was 10.0%, while no major amputations were noted in the claudication subgroup throughout the follow-up period, a fact that further supports the long-term safety of the method.

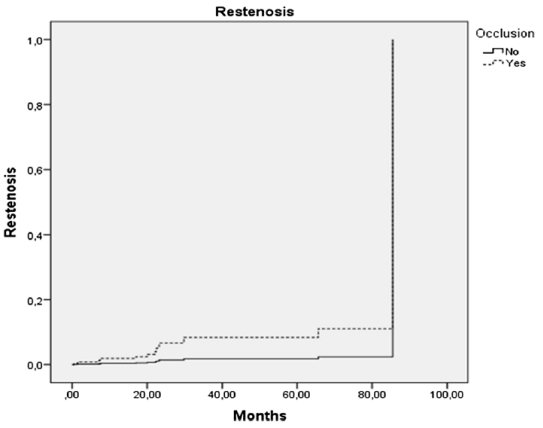

Fig. 2 Cox multivariable analysis plot of target lesion restenosis rate stratified according to baseline lesion grade (stenosis or occlusion)

Limitations of this study include: (1) the retrospective nature of investigation which might have influenced data quality as some parameters such as ABI values and wound healing data could not be retrieved in the majority of the patients and therefore were not reported, while a small number of cases might have been missed (2) the single-arm design, which does not allow treatment comparisons and (3) the relatively small number of patients which certainly reduces the credibility of both univariate subgroup and multivariable analysis in detecting factors associated with outcomes. Nonetheless, Kaplan–Meier analysis should be considered statistically sound, at 3 years for restenosis and TLR-free interval and at 5 years for amputation and survival as the SE remained below 10% at these specific timepoints. (4) The multicenter retrospective design did not allow for a uniform protocol for the detection of restenosis and as a result two different imaging modalities (DUS or DSA) have been implemented. (5) The statistical value of outcomes at 3 years and beyond was significantly decreased for restenosis and TLR and therefore data are not presented, while the 5-year survival outcome is restricted by the fact that numbers at risk decreased to 9.

In conclusion, according to the results of this multicenter study, IPAD is an uncommon subgroup of PAD. The treatment strategy of plain balloon angioplasty and bail-out stenting resulted in acceptable long-term clinical outcomes. Treatment of occlusions was correlated with increased restenosis rate. In light of the fact that newer and more expensive endovascular technologies have been emerged for the management of popliteal disease, these data certainly merit further investigation with larger, prospective, randomized trials in order to establish the appropriate endovascular treatment protocol for IPAD.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Procedural informed consent was obtained from all individual participants included in the study.

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MEDICAL PHYSICS

Occupational exposure during endovascular aneurysm repair (EVAR) and aortoiliac percutaneous transluminal angioplasty (PTA) procedures

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Abstract

Objectives The purpose of this study was to determine the radiation exposure of primary interventionalist's different body parts during endovascular aneurysm repair (EVAR) procedures and aortoiliac percutaneous transluminal angioplasty (PTA) procedures and to evaluate the efficacy of a radioprotective drape.

Methods Occupational doses for 36 consecutive aortoiliac PTA procedures and 17 consecutive EVAR procedures were estimated using thermoluminescence dosimetry (TLD) chips (TLD-200, Hashaw, Solon, OH). Effective dose (ED) was calculated using the Niklason algorithm. For the evaluation of a 0.25 mm Pb equivalent drape (Ecolab, Saint Paul, Minnesota, USA), experiments were performed using two physical anthropomorphic phantoms (Rando-Alderson Research Labs, CA, USA).

Results Median ED for a typical EVAR and PTA procedure was 4.7 ± 1.4 μSv and 4.4 ± 3.6 μSv, respectively. The highest radiation doses were measured for the operator's hands in both procedures. Moreover, considerable doses were measured to the operator's head, eye lenses and thyroid. Due to the use of the drape, radiation exposure of primary operator's abdominal area, genitals, thyroid and eye lenses was reduced by an average of 59%, 60%, 65% and 59%, respectively. However, dose area product (DAP) and peak skin dose (PSD) were increased by 20% when part of the drape was placed into the X-ray field.

Conclusion During EVAR and PTA procedures, primary operator's organs are exposed to considerable radiation doses. Occupational radiation exposure can be reduced significantly with the proper use of a radioprotective drape.

Keywords Occupational radiation exposure · Radioprotective drapes · Fluoroscopy · Dosimetry · EVAR · PTA

Introduction

Atherosclerosis of aortoiliac arteries, abdominal aorta and below the knee arteries can cause intermittent claudication, gangrene, limb ischemia and loss of a limb [1–3]. Symptoms of peripheral artery disease include rest pain, leg numbness, weak pulse in the lower extremities, coldness on lower leg or feet. PTA is the most common fluoroscopically guided intervention for the treatment of peripheral artery disease [4].

The most frequent form of aortic aneurysm is the abdominal aortic aneurysm (AAA) [5]. Low blood pressure, abdomen pain and death are some of the consequences of a ruptured aneurysm [6]. Repair of AAAs is recommended when the diameter of the aneurysm is greater than 5.5 cm and 5 cm for males and females, respectively [6]. Patients with an abdominal aortic aneurysm can be treated with either open surgery or endovascular surgery. EVAR is a fluoroscopically guided procedure with lower morbidity and mortality rates than the open surgery [7, 8].

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Care of vascular diseases with fluoroscopically guided interventions reduces the duration of stay in hospital as well as morbidity and mortality of patients [7–9]. However, the use of fluoroscopy in PTA and EVAR procedures leads to considerable radiation doses for interventionalists. Only a few studies have evaluated the radiation exposure of primary operator's radiosensitive organs such as thyroid or eye lenses during these procedures. The aim of our study was to determine the radiation exposure of primary interventionalist's different body parts during EVAR and PTA procedures. The efficacy of a radioprotective drape was also evaluated.

Materials and methods

Dosimetric data for 36 consecutive aortoiliac PTA procedures and 17 consecutive EVAR procedures were collected prospectively. The procedures were performed by three experienced interventionalists.

The following data were recorded for all patients: total fluoroscopy time, DAP, PSD and the number of digital subtraction angiography (DSA) series. For each DSA, the angulation of the C-arm, tube potential, DAP, PSD and filtration were also recorded. Positioning of the C-arm in left/right (LAO/RAO) direction was between 0° and 45° for both procedures.

Occupational doses in both procedures were determined using thermoluminescence dosimetry (TLD) chips (TLD-200, Hashaw, Solon, OH). TLDs were calibrated with the use of a radiographic system and an ionization chamber (Radcal Corporation, California, USA). One hundred and twenty TLDs were used. Operators were equipped with 0.5 mm Pb equivalent aprons, protective eyewear and thyroid collars. At the beginning of each procedure, TLD chips were placed on the left side of the head, on the protective eyewear, over and underneath the thyroid collar, on chest level over and underneath the apron and on the middle finger of both hands of the primary operator. The operating room was equipped with both a ceiling-suspended transparent shield and a lead curtain underneath the patient table.

Effective dose (ED) was calculated using the Niklason algorithm [10].

$$E = 0.02\,(H_{OC} - H_{UA}) + H_{UA} \quad (1)$$

where HOC is the dose over the thyroid collar and HUA is the dose under the apron. Estimation of the effective dose with this algorithm is independent of apron's thickness.

To evaluate the efficacy of a radioprotective drape, experiments were performed using two physical anthropomorphic phantoms (Rando-Alderson Research Labs, CA, USA) and a 0.25 mm Pb equivalent drape (Ecolab, Saint Paul, Minnesota, USA). The phantom operator was placed in the position of the primary operator. The second phantom was oriented in the head-first supine position on the operating table. In each experiment, 16 thermoluminescence dosimeters were placed on the phantom operator in the following body regions: forehead, right and left side of the head, right and left eye, neck, abdominal and thoracic region, genitals (Fig. 1).

Three experiments were performed to evaluate the effect of drape positioning on automatic exposure control (AEC) system. In the first case, the drape was not placed into the field. In the second case, the drape was placed slightly into the field and in the third case, about half of the drape was placed into the field (Fig. 2). Total fluoroscopy time and the number of DSA runs were the same for all simulations.

Statistical analysis

Statistical analysis was performed using Prism Software (Graphpad, CA, USA), and Office Excel (Microsoft, WA, USA). D'Agostino's K-squared tests were used to determine the distribution of the acquired values. Spearman rank correlation tests were used to evaluate the degree of association between radiation exposures measured at different body parts of the primary operator and fluoroscopy time. Mann–Whitney U tests were used for the comparison of the values between EVAR and PTA procedures. A P value lower than 0.05 indicates a significant difference between the compared values.

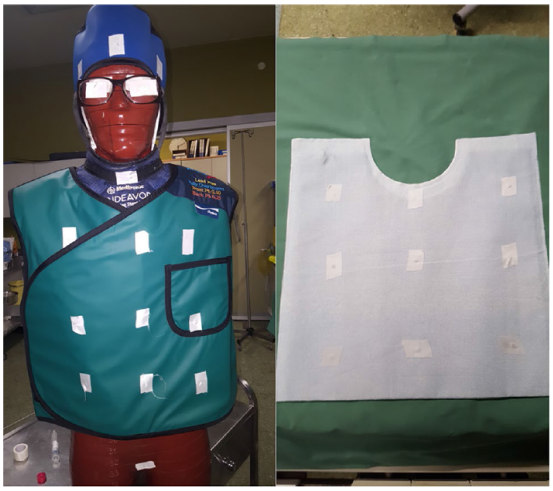

Fig. 1 TLDs placed on Rando anthropomorphic phantom and on drape

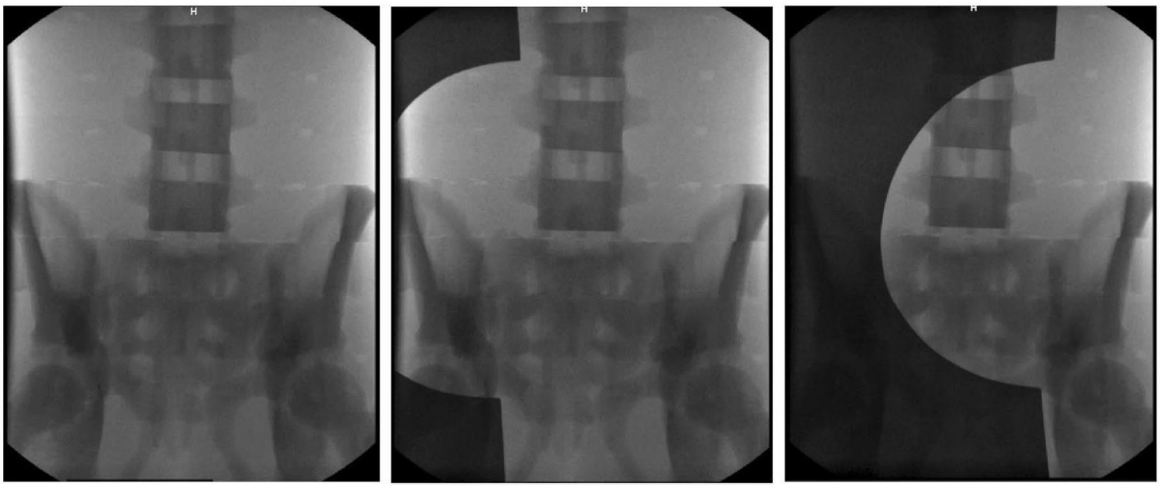

Fig. 2 Positioning of the drape in the first experiment (left), second experiment (middle), third experiment (right)

Results

There was a statistically significant difference in fluoroscopy time ($P = 0.0008$) and DAP ($P < 0.0001$), between PTA and EVAR procedures (Table 1).

Table 2 presents occupational doses of the primary operator, for EVAR and PTA procedures, respectively. The highest radiation doses were measured for the hands of the operator in both procedures. Correlation between radiation exposures measured at different body parts of the interventionalist and fluoroscopy time were ranged from 0.39 to 0.57 (P value ranged from < 0.001 to 0.03) for PTA procedures and from 0.70 to 0.82 ($P < 0.001$) for EVAR procedures. Figures 3 and 4 show the correlations between chest dose over the apron, right-hand dose, thyroid dose over the collar, eye lens dose and fluoroscopy time for the primary operator in PTA and EVAR procedures.

Table 3 presents the maximum number of EVAR or PTA procedures an interventionalist can perform annually. The calculated maximum workloads were based on the annual effective dose limit and equivalent dose to the lens of the eye limit recommended by ICRP as well as on median ED and eye lens doses presented in Table 2.

The results of this study show that the drapes significantly contribute to the operator's radioprotection. Specifically, radiation exposure of the abdominal area, genitals and thyroid, was reduced by an average of 59%, 60%, 65%, respectively, due to the use of the drape. Table 4 presents the reduction at different angulations of the C-arm and at the different body parts. However, drapes should be used with caution, as their misplacement increases exposure parameters, patient dose and occupational dose when AEC is activated. DAP and PSD were subtly different when the drape was placed slightly into the field. On the contrary, differences up to 20% were noted when half of the drape was placed into the field (Table 5).

Discussion

DAP and fluoroscopy time are directly related with the radiation exposure of the interventionalists. Tables 6 and 7 present fluoroscopy time and DAP reported in the literature for EVAR and PTA procedures, respectively. The large variation of the reported values can be attributed to the patient positioning and body characteristics, fluoroscopic equipment as well as operator's skills, training and experience [11, 12].

Table 1 Median Values of Radiation Exposure Parameters for PTA and EVAR procedures

Parameter	Procedure	Value			
		Median	SD	Range	P value
Fluoroscopy time (min)	EVAR	24.5	14.3	13.6–64.7	0.0008
	PTA	14.1	17.9	4.7–88.9	
Total DAP (Gy cm^2)	EVAR	124.3	156.9	41.4–627.1	< 0.0001
	PTA	23.1	61.2	37.0–296.0	

Table 2 Occupation doses of primary operator for EVAR and PTA procedures

Procedure	Median (μGy)	SD	ED (μSv)	Range
EVAR			4.7 ± 1.4	1.5–19.6
Body part				
Head	35.7	37.4		5.8–132.1
Eyes	34.4	37.6		8.3–125.3
Chest (over the apron)	72.6	62.3		10.5–244.4
Chest (underneath the apron)	4.2	3.8		1.5–17.8
Thyroid (over the collar)	25.7	27.5		2.6–107.0
Thyroid (underneath the collar)	5.9	6.5		1.6–30.2
Left hand	76.9	111.9		13.3–418.7
Right hand	46.7	122.7		8.7–520.5
PTA			4.4 ± 3.6	1.0–11.0
Body part				
Head	10.6	27.1		3.4–141.8
Eyes	12.3	41.3		3.1–211.2
Chest (over the apron)	14.8	69.5		4.4–297.9
Chest (underneath the apron)	4.3	1.6		0.9–7.5
Thyroid (over the collar)	10.9	38.8		3.9–178.6
Thyroid (underneath the collar)	4.8	2.5		1.0–10.7
Left hand	39.6	355.0		4.9–1877.5
Right hand	22.4	143.2		2.7–636.2

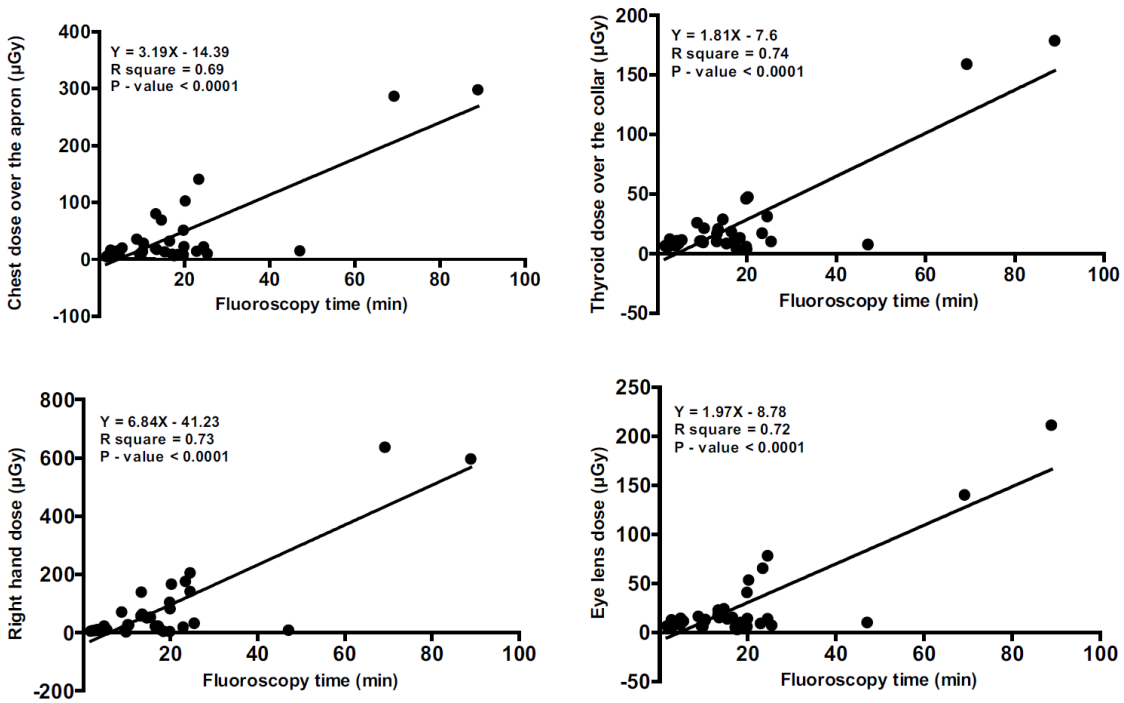

Fig. 3 Correlations between different body parts doses and fluoroscopy time in PTA procedures

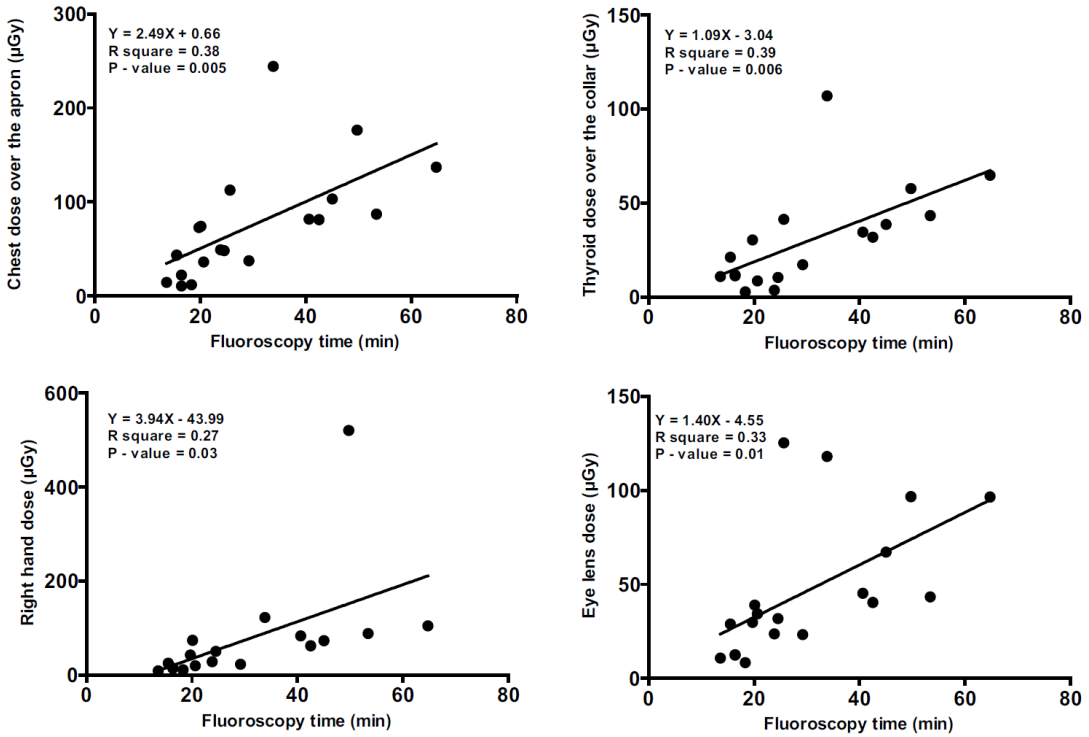

Fig. 4 Correlations between different body parts doses and fluoroscopy time in EVAR procedures

Table 3 Maximum permissible annual workload based on ED and eye lens doses

Procedure	Number of procedures (based on ED)	Number of procedures (based on eye lens dose)
EVAR	4255	581
PTA	4545	1626

Tabulated data (Table 2) show that radiation exposure of the primary operator was higher in EVAR procedures than in PTA procedures. The highest radiation doses were measured for the operator's hands in both procedures. To the best of our knowledge, only two studies, Neto et al. [13] and Ho et al. [14], reported hand doses for the primary operator during EVAR procedures. Specifically, Ho et al. [14] reported a median hand dose of the chief surgeon equal to 34.3 µSv, while the respective dose reported by Neto et al. [13] was 2105.3 µSv. The right- and left-hand doses of the primary operator, presented in the current study, were 46.7 µSv and 76.9 µSv, respectively. Based on the literature, hand doses of the interventionalists during PTA procedures range from 21 to 190 µSv [13–15, 23, 24].

Eye lens doses during PTA procedures have been evaluated by a number of studies [13–15, 23–25]. The reported doses vary from 2.0 to 53.7 µSv. The wide range of these values indicates that several parameters including complexity of the procedures as well as the experience of the operator affect the radiation exposure of the interventionalists. The number of studies reporting eye lens doses during EVAR procedures is relatively small. The lower eye lens dose per EVAR procedure (9.7 µSv) has been reported by Ho et al. [14]. This is 3.5 times lower than the respective dose presented herein. Of note, however, is that Ho et al. [14] placed the dosimeters within lead eyeglasses while we placed them externally. Concerning thyroid, high doses, i.e., 338.4 µSv and 58.8 µSv for EVAR and PTA procedures, respectively, were measured above the collar by Neto et al. [13]. These are 13.2 and 5.4 times higher than the corresponding values presented herein. These differences may be attributed to the absence of a ceiling-suspended transparent shield.

The proper use of a radioprotective drape leads to a significant reduction in occupational doses. The current study shows that the use of a drape reduces the eye lens dose to primary operator by an average of 59%. Significant reduction in the radiation exposure was also recorded for the abdominal

Table 4 Reduction of the radiation exposure with the use of a radioprotective drape

Angulation of the arm			Percentage differences between radiation doses measured at different body parts with and without the radioprotective drape													
LAO	CRA	CAU	Right side of the head	Forehead	Left side of the head	Right Eye Lens	Left Eye Lens	Thyroid	Right HR	Right LR	Right IR	EPR	UMR	HGR	Left HR	Left LR	Left IR	Genitals
0°	0°	0°	17	38	47	43	47	53	18	41	36	26	45	31	43	37	36	52
15°	0°	0°	43	51	50	38	39	56	53	48	45	59	57	47	57	59	55	67
0°	15°	0°	27	77	74	78	76	75	74	80	73	69	77	76	76	74	74	56
0°	0°	15°	27	75	67	76	75	75	74	76	75	68	77	70	70	73	71	66

HR hypochondriac region, *LR* lumbar region, *IR* iliac region, *EPR* epigastric region, *UMR* umbilical region, *HGR* hypogastric region, *LAO* left anterior oblique, *CRA* cranial angulation angle, *CAU* caudal angulation angle

Table 5 Differences in DAP and PSD due to the placement of the drape into the field

Position of the drape	DAP (μGym^2)	PSD (mGy)
Out of the field	2218.3	88.9
Slightly into the field	2221.4	89.6
Half of the drape into the field	2769.6	111

Table 6 Reported total fluoroscopy time (FT) and DAP during EVAR procedures

Study	FT (min)	DAP (Gy cm^2)	Comments
Patel et al. [18]	19.5	97.3	
Sailer et al. [19]	19.6	116	
Hertault et al. [20]	27.3	41.2	
Ho et al. [14]	13.0	–	
Neto et al. [13]	29.3	–	
Blaszak et al. [21]	19.6	354.0	
Tuthill et al. [22]	13.1	31.6	Site A
	11.7	184.2	Site B
	9.0	80.2	Site C
	14.6	60.8	Site D
	11.2	162.5	Site E
This study	24.5	124.3	

Table 7 Reported total fluoroscopy time (FT) and DAP during PTA procedures

Study	FT (min)	DAP (Gy cm^2)
Heye et al. [23]	6.2	4.1
Ingwersen et al. [24]	7.2	–
Jensen et al. [25]	13.0	24.0
Ho et al. [14]	6.3	–
Neto et al. [13]	15.6	–
Power e al. [15]	8.2	24.6
Sigterman et al. [26]	13.0	108.0
McBridge et al. [27]	15.6	–
This study	14.1	23.1

region, thyroid and genitals. Further, a mean reduction up to 29%, 60%, and 60%, of the radiation exposure, was recorded for the right side of the head, the forehead and the left side of the head, respectively. These results are in agreement with the corresponding results presented in the literature [15–17].

The efficacy of the drape has been evaluated by a number of studies. To the best of our knowledge, this is the first study examining the effect of the positioning of drapes on AEC. Our results show that activation of AEC yields higher radiation dose for patients and personnel when the drape is included in the field. Specifically, DAP and PSD were

increased by 20% when part of the drape was placed into the X-ray field. Radiation dose increases when a drape is in the X-ray field because AEC increases the exposure in an attempt to maintain image quality.

Our study has some limitations that should be considered. First, it was a single-center study. All measurements were taken in a specific interventional radiology suite. Second, the effect of procedural complexity on occupational doses, fluoroscopy time and DAP was not examined. Third, the evaluation of the radioprotective drape was carried out using physical anthropomorphic phantoms. A patient study is needed to confirm the effect of the drapes positioning on AEC.

Conclusion

During EVAR and PTA procedures, primary operator's organs are exposed to considerable radiation doses. The highest radiation doses were measured for the operator's hands in both procedures. Occupational radiation exposure can be reduced significantly using a radioprotective drape. However, the use of the drape needs caution as its misplacement could lead to higher doses for the patients and the operators.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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ANGIOPLASTY VERSUS BYPASS FOR THE TREATMENT OF PATIENTS WITH TISSUE LOSS DUE TO INFRAINGUINAL PERIPHERAL ARTERY DISEASE. AN INTENTION-TO-TREAT ANALYSIS

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THE USE OF STENT-GRAFTS AFTER LOOP ENDARTERECTOMY FROM ILIOFERMORAL AND FEMORAL-POPLITEAL SEGMENTS IN PATIENTS WITH ATHEROSCLEROTIC INJURY OF VESSELS IN LOWER EXTREMITIES

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THE IMPACT OF PERIPHERAL ARTERIAL DISEASE ON THE OUTCOME OF PATIENTS PRESENTING AS DIABETIC FOOT EMERGENCIES TO A VASCULAR SURGERY UNIT

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ONE YEAR RESULTS OF SUBINTIMAL ANGIOPLASTY

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BEST MEDICAL THERAPY IN LOWER LIMB PERIPHERAL ARTERIAL DISEASE

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ENDOVASCULAR TREATMENT OF CHRONIC TOTAL OCCLUSIONS OF THE ILIAC ARTERIES

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