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Contents

Editorial

Mixed reality: a promising technology for Therapeutic Patient Education

Comment on J. Hatzl et al., pp. 160–168

Cristina Lopez-Espada[1,2,3] and Jose Linares-Palomino[1,2,3]

[1] Vascular Surgery Unit, University Hospital Virgen de las Nieves, Granada, Spain
[2] Instituto de Investigación Biosanitaria ibs. Granada, Spain
[3] Department of Surgery, School of Medicine, University of Granada, Spain

In 1989, the European office of the World Health Organization (WHO) defined *Therapeutic Patient Education* (*TPE*) as: "the set of measures that enables people with chronic diseases to manage their illness and yields benefits in both health and financial terms" [1]. However, it was also warned "many healthcare providers (HCP) lack of skills to provide their patients with such an education".

The paper by Hatlz and colleagues from the University of Heidelberg is commendable in this respect [2]. A teaching method based on the latest available technology (mixed reality) is implemented in patients who will undergo infrarenal aortic aneurysm surgery. This new technology is compared with the conventional educational process.

On many occasions, patients are offered limited information regarding their surgical procedure, enough to obtain a legally impeccable written informed consent. International health care organizations and stakeholders have recommended their use in routine patient care and this policy has been proven to modify health behaviour positively and thus, improve biological, psychological, and quality of life outcomes for many patients with chronic disorders [3, 4]. The evidence suggests that educated patients develop skills to better manage and adapt their lives to their disease [5].

These educational programs have been developed in a very asymmetrical pattern in patient care. Some well-designed programs have been applied to many chronic diseases such as diabetes, cancer, heart disease, or psychiatric diseases [2]. However, the TPE is less implemented in surgical procedures [6]. In Vascular Surgery and Angiology, most of its etiological conditions are chronic, such as arteriosclerosis. This might justify the implementation of powerful TPE programs, as stated in the paper by Hatzl et al. An aortic aneurysm is a surgical condition with high mobility and mortality. Surgery can prevent patient from dying with a ruptured aneurysm, but also compel the patient to a strict surveillance program lifelong. In this type of vascular diseases, the involvement of patients in self-care can improve their health condition. Education should range from the effective control of risk factors (smoking cessation, hypertension and diabetes levels) to the need of modifying the patient's lifestyle. These patients should also be educated on their dependence on life-long medication consumption, compliance to surveillance programs after surgery and also in the awareness of postoperative complications [7].

Hatzl's paper has shown that there are many features involved in the TPE process. Special consideration should be given to the primary assessment of the patient and the competence of the trainers. When a patient is first assessed, it would be necessary to consider: age, chronic conditions, years of disease evolution and treatment/s, patient knowledge, technical skills, attitudes, socio-cultural situation, quality of life perception and adherence to treatment.

As in Hatzl's study, patients suffering from an abdominal aortic aneurysm (AAA) tended to be fragile, elderly, with a reduction in their learning capacities and with a high surgical risk (ASA risk >3). Most of them were patients on lifelong medication for chronic diseases, such as diabetes (20%), coronary arterial diseases (46%), hypertension (92%) and being active smokers.

In light of the above, it is essential to design an educational program, flexible enough to adapt to the great variability of the primary conditions of the patients, including the level of anxiety when facing of imminent surgery [6, 7].

The second factor to be considered is the quality of the training and the competence of the trainers. TPE can be provided by HCP responsible of a patient with a chronic disease, by a nurse or physician responsible of the surgical follow-up or by other professionals such as psychologist, or social worker. All of them can contribute directly to the educational process.

Patient-centred communication techniques are accessible to a wide range of professionals. Using a variety of educational techniques, patients are allowed to commit to an active learning process within an individually tailored programme. The quality of TPE activities depends to a large extent on the abilities, skills and training of HCPs [5, 8]. According to this, the mixed reality methodology followed

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by Hatzl is an interesting aid for TPE. TPE has been proposed to be part of HCP training programs [1, 6, 8].

According to the current study of Hatzl's group, both strategies followed in TPE (traditional and mixed reality) increase the level of patient's knowledge about the disease and the perceived quality satisfaction and also demonstrate that elderly patients do not reject the use of virtual technology (Head-mounted Display) despite their serious chronic conditions and the concern about their near coming surgical intervention. The use of virtual glasses did not have a negative impact in patients or distracted them from the learning task, as other authors have shown [9, 10].

In summary, this publication by Hatzl et al. significantly improves the TPE methodology. Their initiative empowers patients to control their health and also reinforce specific training programs to increase competence of HCPs in the process of patient health care education.

References

1. World Health Organization. Europe Report Therapeutic Patient Education – Continuing Education Programmes for Health Care Providers in the Field of Chronic Disease. Copenhagen, Denmark: WHO; 1998.
2. Hatzl J, Hartmann N, Böckler D, Henning S, Peters AS, Meisenbacher K, et al. Mixed Reality in patient education prior abdominal aortic aneurysm repair – A prospective, randomized, controlled pilot study. Vasa. 2023;52(3):160–8.
3. Correia JC, Waqas A, Aujoulat I, Davies MJ, Assal JP, Golay A, et al. Evolution of therapeutic patient education: a systematic scoping review and scientometric analysis. Int J Environ Res Public Health. 2022;19(10):6128–54.
4. Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA. Diabetes patient education: a meta-analysis and meta-regression. Patient Educ Couns. 2004;52:97–105.
5. Pétré B, Gagnayre R, De Andrade V, Ziegler O, Guillaume M. From therapeutic patient education principles to educative attitude: the perceptions of health care professionals – a pragmatic approach for defining competencies and resources. Patient Prefer Adherence. 2017;11:603–17.
6. Jansà M, Bertran MJ, Vilardell J, Garcia F, Escarrabill J. Working Group on Information and Therapeutic Education (GTIET) of the Hospital Clínic de Barcelona. Analysis of the quality of patient therapeutic education and information in a high complexity reference hospital. J Healthc Qual Res. 2018;33:343–51.
7. Haute Autorité de Santé. Therapeutic Patient Education (TPE): Definition, goals, and organisation. Saint-Denis La Plaine Cedex: Haute Autorité de Sante; June 2007. Available from: https://www.has-sante.fr/jcms/c_728236/fr/therapeutic-patient-education-tpe-definition-goals-and-organisation-quick-reference-guide
8. Deccache A, Aujoulat IA. European perspective: common developments, differences and challenges in patient education. Patient Educ Couns. 2001;44:7–14.
9. Jensen L, Konradsen F. A review of the use of virtual reality head-mounted displays in education and training. Educ Inf Technol. 2018;23:1515–29.
10. Găină MA, Szalontay AS, Ştefănescu G, Bălan GG, Ghiciuc CM, Boloş A, et al. State-of-the-art review on immersive virtual reality interventions for colonoscopy-induced anxiety and pain. J Clin Med. 2022;11:1670–81.

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ORCID
Cristina Lopez Espada
https://orcid.org/0000-0002-6157-7829

Correspondence address
Cristina López Espada, MD, PhD, FEBVS
University Hospital Virgen de las Nieves
Instituto de Investigación Biosanitaria ibs. Granada
Avenida Fuerzas Armadas 2
18014 Granada
Spain

clegra3@hotmail.com

Position paper

Endovascular interventions in outpatient care

Statement paper of the German Society of Angiology (DGA) – Society for Vascular Medicine e.V.

Marcus Thieme[1,2,3], Hans Krankenberg[1,3], Tom Schilling[4], Stefan Betge[5], Grigorios Korosoglou[6], Christos Rammos[7], Markus Vosseler[8], Christine Espinola-Klein[8], Britta Heilmeier[9], Oliver J. Müller[10], Ralf Langhoff[11], Nasser Malyar[12], Erwin Blessing[13], Lutz Caspary[14], Birgit Linnemann[15], Christian Heiss[16,17], and Wulf Ito[18] for the DGA – German Society of Angiology Board and ESVM – European Society of Vascular Medicine Board

[1] Regiomed Vascular Center and Department of Internal Medicine, REGIOMED-Hospital GmbH, Sonneberg, Germany
[2] Department of Internal Medicine I, University Hospital Jena, Germany
[3] School of Medicine, University of Split, Croatia
[4] Center for Internal Medicine, Harz-Hospital Wernigerode, Germany
[5] Department of Internal Medicine and Angiology, HELIOS-Hospital Salzgitter, Germany
[6] Department of Cardiology and Angiology, GRN Hospital Weinheim, Germany
[7] Department of Cardiology and Angiology, University Hospital Essen, Germany
[8] Center for Cardiology, University Hospital Mainz, Germany
[9] Vascular Practice im Tal, Munich, Germany
[10] Department of Internal Medicine III, University Hospital Schleswig-Holstein, Kiel, Germany
[11] Department of Angiology, St. Gertrauden Hospital, Berlin, Germany
[12] Department of Cardiology I, University Hospital Münster, Germany
[13] Department of Vascular Medicine, University Hospital Hamburg, Germany
[14] Vascular Practice, Hannover, Germany
[15] Department of Angiology, University Vascular Center East Bavaria, University Hospital Regensburg, Germany
[16] Department of Clinical and Experimental Medicine, University of Surrey, Guildford, UK
[17] Vascular Department, Surrey and Sussex Healthcare NHS Trust, Redhill, UK
[18] Heart and Vascular Center, Allgäu Hospital gGmbH, Immenstadt, Germany

Summary: Endovascular arterial revascularisations for the treatment of symptomatic peripheral arterial disease are constantly increasing in importance and number due to the changing age structure and high numbers of comorbidities in the German population. Patients with peripheral artery disease are often at increased risk for peri- and post-procedural complications including severe cardiovascular events. Due to limited financial and human resources and considerable risks of hospitalization, endovascular interventions that were previously reserved for hospitalized patients are now progressively considered to be performed as day case procedures. More than one third of these procedures are performed in Germany by internists with a specialization in angiology. In the current position paper the German Society of Angiology endorsed by the European Society of Vascular Medicine, summarizes the requirements and risk factors to be considered for the planning, safe performance and post procedural care of endovascular revascularizations in outpatients. The performance of endovascular procedures for peripheral artery disease both in hospitalised and outpatients should be accompanied by a mandatory quality assurance process that should not only capture procedural data, but also require documentation of complications and longterm outcome.

Keywords: Daycase, endovascular, angioplasty, peripheral artery disease, Germany, same day discharge

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Introduction

The German Society for Angiology (DGA) was founded in 1972 as a scientific specialist society for vascular medicine. Since 1992, the medical speciality of angiology has been recognised as a board-certified internal medicine sub-speciality in Germany. In addition to the comprehensive medical diagnosis and conservative therapy of vascular diseases as well as the management of risk factors and concomitant diseases, endovascular interventions are part of the core competence of angiologists. In the German medical Continuing Professional Education regulation, they are firmly embedded in the training to become a board-certified specialist in internal medicine and angiology. The certification of the curriculum "Interventional Therapy of Arterial Vascular Diseases" guarantees the performance of endovascular interventions according at a high, recognised and defined standard by an angiologist, certified for this purpose [1].

In particular peripheral arterial disease is closely related to other medical conditions such as diabetes mellitus, arterial hypertension or dyslipidaemia. At the same time, peripheral arterial disease is associated with markedly increased cardiovascular mortality [2]. As an internist, it is the primary task of the specialist for internal medicine and angiology to place endovascular therapy always in the context of the general state of health of the patients, who often additionally suffer from other severe comorbidities. It is therefore not surprising that according to the quality reports of hospitals in Germany, published by the Federal Joint Committee in 2018, approximately one-third of all inpatient peripheral endovascular interventions were carried out by angiologists/internists, indicating the central role of angiology, as the primary discipline, which is in charge of the clinical care and endovascular treatment of such patients. Therefore, the German Society of Angiology herewith takes a position on safe implementation of outpatient endovascular vascular procedures.

Due to technical progress, endovascular interventions have gained increasing importance in the last decade, especially in the treatment of arterial diseases [3]. In addition, it has been shown that a delay in endovascular revascularisation leads to a higher amputation rate [4]. However, so far, these interventions have only rarely been performed in an outpatient setting in Germany. A recent interim analysis of the Quality Registry of the German Society of Angiology (Recording Courses of Vascular Diseases, RECCORD; ClinicalTrials.gov, Identifier: NCT03448029) revealed that currently only 3.4% of endovasclar revascularisations are performed as day cases in Germany. The registry includes reporting of clinical and procedural data including complications of patients after endovascular revascularisations of the lower extremity. It documents a high technical success rate of 96% and a low total complication rate of 5.8% in outpatients. The criteria for day case vs. inpatient selection were not recorded in the registry. The German Society of Angiology basically encourages the option of outpatient care for endovascular interventions in favour of the economical use of the limited resources in the health sector. However, patient safety should have the highest priority for individual decision-making. Accordingly, the following statement focuses mainly on this aspect.

Several studies in recent years have shown high technical success and low complication rates for endovascular procedures. These results serve as the basis for this position paper. In elective outpatient endovascular interventions with a low degree of complexity, the technical success rate is 92% [5, 6]. With a careful patient selection, post-interventional hospitalisation is to be expected in only 0.5–0.7% [5]. The perioperative major complication rate of outpatient vascular interventions is similar to that of inpatient interventions (haematoma requiring intervention: 0.3%, stenosis/occlusion: 0.2%, distal embolization: 0.9%) [7]. For a period of 3 years, it could be shown that complication rate, the number of revascularisations, the amputation rate, and overall mortality is comparable between outpatient and inpatient care [8].

The Vascular Quality Initiative PVI Registry showed that a careful patient selection is necessary: in over 127,000 patients treated as outpatients or inpatients between 2010 and 2021, differences in patient populations, indications, and types of interventions were significantly different between both forms of care. However, complication rates were similarly low [7].

A checklist with a decision pathway for pre- and post-intervention evaluation of patients for whom outpatient vascular intervention may be considered is shown in figure 1.

Requirements for outpatient peripheral vascular interventions

Based on the scientific data available to date, the following patient characteristics are to be assumed regarding the highest possible level of patient safety in outpatient vascular interventions:

General conditions for outpatient peripheral vascular interventions

- Consent of the patient.
- Sufficient general condition, clinical stability (not older than 80 years, not frail, without severe pronounced overweight or underweight) [9, 10, 11].
- Sufficient cognitive function and compliance.
- Sufficient mobility in the home environment.
- Domestic conditions that ensure safe follow-up care, having a responsible adult to stay with them.
- No pronounced fear of complications.
- Timely accessibility of medical assistance in case of complications (travel time less than 30 minutes).
- Transportation to preliminary and follow-up examinations possible.
- Sufficiently possible pre-interventional outpatient diagnostics.

Pre-Procedure Evaluation

Patient Factors: Clinical	1. Is the patient experiencing an acute or a chronic limb-threatening ischemia?	☐ No ↓	☐ Yes →	Monitor patient overnight
	2. Does any member of the care team feel for any other reason that the patient is not a candidate for same-day discharge?	☐ No ↓	☐ Yes →	
Patient Factors: Social	3. Does the patient have adequate caregiver support?	☐ Yes ↓	☐ No →	
	4. Can the patient or caregiver reach 112, if necessary?	☐ Yes ↓	☐ No →	
	5. Is the patient willing to be discharged the same day (shared decision-making)?	☐ Yes ↓	☐ No →	
Staff/System Factors	6. Is the patient scheduled early enough in the day so that he/she can be observed for a sufficient amount of time (4-6 hours post-procedure) and discharged at a reasonable time?	☐ Yes ↓	☐ No →	

Care Team Action ←
Once the procedure is finished, complete the Post-Procedure Evaluation on the next page to confirm same-day discharge.

Post-Procedure Evaluation

7. Did complications occur during the procedure?	☐ No ↓	☐ Yes →	Monitor patient overnight
8. Was the intervention successful?	☐ Yes ↓	☐ No →	
9. Is the patient experiencing any of the following post-procedure? Stroke, bleed, vascular complications, allergic reaction, unresolved and/or severe chest pain, acute heart failure, persistent ischemic ECG changes, dysrhytmia, or any other unforeseen complications.	☐ No ↓	☐ Yes →	
10. Is there an exacerbation of an underlying disease (e.g., heart failure, high blood pressure, diabetes, COPD flare)?	☐ No ↓	☐ Yes →	
11. Is the patient's mental status the same as baseline presentation	☐ Yes ↓	☐ No →	
12. Is the patient willing to be discharged the same day (shared decision-making)?	☐ Yes ↓	☐ No →	

Proceed to the Pre-Discharge Checklist

Figure 1. Pre- and post-procedure evaluation and decision pathway on same-day discharge after endovascular intervention adapted from the American College of Cardiology [19].

Absence of concomitant diseases requiring hospitalisation

- No concomitant diseases requiring secondary inpatient treatment surrounding the procedure.
- No concomitant diseases that increase the risk of systemic complications during the follow-up phase.

No increased intervention- and/or perfusion-associated risk

- No need for inpatient treatment before the start of the examination.
- No known complications from previous catheter interventional procedures.
- No examination result requiring immediate and continuous inpatient monitoring.
- No examination result that could potentially lead to further measures on the following day.
- No persistent – potentially critical – circulatory disorder requiring supplementary conservative follow-up treatment.
- No local findings potentially requiring follow-up interventions (e.g., debridement, minor amputation).
- No increased risk of local complications during the follow-up phase.

Risk factors for peripheral vascular interventions in an outpatient setting

Based on scientific data and the authors' consensus, outpatient vascular intervention is not suggested in the following disease- and/or procedure-related conditions.

Systemic findings

- Frailty in older age (Clinical Frailty Score≥Grade 4) [9, 10, 11].
- Pronounced underweight or overweight (body mass index <18.5 or >35).
- Acute and chronic right and/or left heart failure (in particular NYHA III and IV, severely impaired left ventricular function [LVEF<40%]).
- Severe valvular heart disease.
- Pulmonary hypertension with an invasive mPAP >25 mmHg or non-invasive systolic PA pressure of >50 mmHg.
- Chronic respiratory insufficiency with long-term oxygen therapy, non-invasive ventilation or Continuous Positive Airway Pressure (CPAP) therapy.
- Chronic renal failure from stage II onwards [22].
- Insulin-dependent diabetes mellitus or metabolic disorder [12].
- History of gastrointestinal bleeding.
- Systemic risk of bleeding (hepatic insufficiency, underlying haematological diseases, chronic inflammatory bowel diseases).
- Parkinson's disease or other underlying neurological and neuromuscular diseases.
- Post-stroke condition with residual cognitive, sensory, or motor deficits, cerebrovascular events (haemorrhage, TIA, stroke, embolism <30 d).
- Dementia or other cognitive impairment.
- Underlying psychiatric diseases.
- Mobility-limiting orthopaedic or other diseases.
- Inadequately controlled arterial hypertension with repeatedly documented values >180 mmHg systolic and/or diastolic >110 mmHg.
- Known allergy to contrast media.
- Hyperthyroid metabolic state.
- Comedication contraindicated to concomitant pharmacotherapy.

The risk of serious cardiovascular or limb-related events and all-cause mortality is more than doubled in frail patients with peripheral arterial disease [9, 10, 11]. The outcomes of vascular interventions are also strongly associated with the general condition [13]. In patients with insulin-dependent diabetes, vascular interventions are more often associated with impaired wound healing and major amputation than in non-insulin-dependent patients [12]. Heart failure is a risk factor for severe periprocedural haemorrhage [14].

Characteristics of the underlying vascular disease

- Acute onset or subacute worsening of circulatory disorder [15]
- Chronic limb-threatening ischaemia (Rutherford category ≥4).
- Complicated wound- or infection situations with pre-interventional necessary measures.
- Post-intervention persisting circumstances justifying hospitalisation.
  - o Persistent infection.
  - o Persistent critical wound conditions.

In interventions for acute ischaemia, 10% of patients require periprocedural amputations, with a mortality rate of 20% [15]. Chronic limb-threatening ischaemia is associated with severe periprocedural haemorrhage [14]. The incidence is described as 23%. Periprocedural cardiovascular events occur in 9% of patients. The rate of periprocedural major amputation is 3% and mortality is 4%. In addition, multiple procedures are required in about one third of patients with chronic limb-threatening ischaemia [16].

Intervention-related factors

- Administration of more than 5000 IU heparin.
- Transbrachial access, associated with higher access site complication rates [14].
- Multiple puncture attempts, difficult access, atypical puncture sites.
- Need for mechanical thrombectomy or lysis therapy.
- Periinterventional bleeding, requiring the use of covered stents.
- Necessary non-target lesion examinations (e.g., due to embolism or vasculitis).
- Long procedure time [17].
- Failure to use a vascular closure system with a sheath size of ≥6F.
- Post-examination bleeding.
- Intraprocedural complications.
- Administration of high amounts of contrast medium with the need for IV hydration and close-meshed laboratory tests.

A prospective observational study identified a series of risk factors for bleeding complications associated with vascular interventions that justify the recommendations listed above [18]: For example, the rate of bleeding complications increases with the dose of heparin administered and is significantly increased above 5000 IU (odds ratio [OR] at 5000 IU heparin: 1.96; above 5000 IU: 2.60). In addition, there were significantly more bleeding complications with transbrachial compared to transfemoral access (OR transbrachial versus retrograde transfemoral: 4.58) which often occur several hours after the intervention and require immediate treatment. The administration of thrombolytics is also associated with a significantly increased rate of bleeding complications (OR: 3.56). In addition, a longer examination time is usually an expression of a more complex intervention.

Extending the examination time by 10 minutes increases the rate of access complications by 1% each (OR per 10 minutes: 1.01). The registry further showed that the complication rate decreases significantly with the use of vascular closure devices. Therefore, the use is highly recommended in particular when using sheath sizes above 6F. If the use of vascular closure devices is not possible for patient- or procedure-related reasons, increased bleeding complications must be expected (OR for use of a vascular closure device: 0.80) [18].

Conclusions

Endovascular vascular interventions for the treatment of stable, acute and chronic peripheral arterial disease are constantly increasing in importance and number due to the changing age structure and high numbers of comorbidities in the German population. Patients with peripheral artery disease are often due to their age and multimorbidity at increased risk for peri- and post-procedural complications including severe cardiovascular events. The aspects of risk management and patient safety need to play a major role in the individual decision-making favouring or excluding the possibility of a procedure being performed on an outpatient basis. The focus of this position paper is on patient safety during and after endovascular vascular interventions. Concrete social and medical factors were listed that speak against outpatient post-interventional care. These factors were collected in accordance with Good Clinical Practice, the current medical data situation and the existing guidelines and position papers [20, 21]. The performance of in- and outpatient endovascular procedures for peripheral artery disease should be accompanied by a mandatory quality assurance process that should not only capture procedural data, but also require documentation of complications and long-term outcome. The RECCORD registry of the German Society of Angiology would naturally lend itself for this purpose also allowing comparison of results with procedures performed in hospitalised patients.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a001067

ESM 1. German version of the Statement paper of the German Society for Angiology (DGA) – Society for Vascular Medicine e.V.

References

1. Langhoff R, Schulte KL, Amendt K, Erbel C, Hardung D, Nikol S, et al. Curriculum Interventionelle Therapie der arteriellen Gefäßerkrankungen. Der Kardiologe. 2022;16(2):164–77.
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.
3. Farhan S, Enzmann FK, Bjorkman P, Kamran H, Zhang Z, Sartori S, et al. Revascularization strategies for patients with femoropopliteal peripheral artery disease. J Am Coll Cardiol. 2023;81(4):358–70.
4. Li Q, Birmpili P, Johal AS, Waton S, Pherwani AD, Boyle JR, et al. Delays to revascularization for patients with chronic limb-threatening ischaemia. Br J Surg. 2022;109(8):717–26.
5. Chow CY, Mathlouthi A, Zarrintan S, Swafford EP, Siracuse JJ, Malas MB. Outcomes of elective peripheral endovascular interventions for peripheral arterial disease performed in hospital outpatient departments, ambulatory surgical centers and office-based labs. J Vasc Surg. 2023;S0741-5214(23):00274-4. Epub ahead of print.
6. Rodway A, Stafford M, Wilding S, Ntagiantas N, Patsiogiannis V, Allan C, et al. Day case angioplasty in a secondary care setting – initial experience. Vasa. 2021;50(3):202–8.
7. Haqqani MH, Alonso A, Kobzeva-Herzog A, Farber A, King EG, Meltzer AJ, et al. Variations in Practice Patterns for Peripheral Vascular Interventions Across Clinical Settings. Ann Vasc Surg. 2023S0890-5096(23)00022-5. Epub ahead of print.
8. Giannopoulos S, Pliagas G, Armstrong EJ. Procedural and 3-year outcomes of peripheral vascular interventions performed in office-based labs: LIBERTY 360 sub-analysis. J Invasive Cardiol. 2021;33(5):E365–E77.
9. Li J, Arora S, Ikeoka K, Smith J, Dash S, Kimura S, et al. The utility of geriatric nutritional risk index to predict outcomes in chronic limb-threatening ischemia. Catheter Cardiovasc Interv. 2022;99(1):121–33.
10. Liu G, Zou C, Jie Y, Wang P, Wang X, Fan Y. Predictive value of geriatric nutritional risk index in patients with lower extremity peripheral artery disease: a meta-analysis. Front Nutr. 2022;9:903293.
11. Ruangsetakit C, Navikaputra S, Pruekprasert K, Prapassaro T, Puangpunngam N, Hongku K, et al. The Geriatric Nutritional Risk Index predicts amputation after infrapopliteal angioplasty in critical limb ischemia patients. Asian J Surg. 2023;46(1):250–3.
12. Darling JD, Bodewes TCF, Deery SE, Guzman RJ, Wyers MC, Hamdan AD, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia between patients with and without diabetes. J Vasc Surg. 2018;67(4):1159–69.
13. Yamaguchi T, Ueshima D, Utsunomiya M, Matsui A, Miyazaki T, Matsumoto M, et al. Optimal cut-off value of preprocedural geriatric nutritional risk index for predicting the clinical outcomes of patients undergoing endovascular revascularization for peripheral artery disease. J Cardiol. 2021;77(2):109–15.
14. Salisbury AC, Safley DM, Kennedy KF, Bhardwaj B, Aronow HD, Jones WS, et al. Development and validation of a predictive model for bleeding after peripheral vascular intervention: a report from the National Cardiovascular Data Registry Peripheral Vascular Interventions Registry. Catheter Cardiovasc Interv. 2021;98(7):1363–72.
15. Juneja A, Garuthara M, Talathi S, Rao A, Landis G, Etkin Y. Predictors of poor outcomes after lower extremity revascularization for acute limb ischemia. vascular. 2023.17085381231154290. Epub ahead of print.
16. Compagnon A, Lazareth I, Fels A, Chatellier G, Emmerich J, Michon-Pasturel U, et al. Peri-procedural complications following endovascular revascularization for critical limb ischemia. J Med Vasc. 2022;47(4):175–85.
17. Ostapenko A, Stroever S, Dietzek AM. Prolonged lower extremity endovascular procedures for patients with claudication increase risk of adverse outcomes. J Vasc Surg. 2022;76(6):1681–7.e1.
18. Ciprian Cacuci A, Krankenberg H, Ingwersen M, Gayed M, Stein SD, Kretzschmar D, et al. Access site complications of peripheral endovascular procedures: a large, prospective registry on predictors and consequences. J Endovasc Ther. 2021;28(5):746–54.

19. Rao SV, Vidovich MI, Gilchrist IC, Gulati R, Gutierrez JA, Hess CN, et al. 2021 ACC expert consensus decision pathway on same-day discharge after percutaneous coronary intervention: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):811–25.
20. Reinecke H, Braun M, Frankenstein L, Görge G, Kerlin A, Knoblich S, et al. Kriterien für die Notwendigkeit und Dauer von Krankenhausbehandlungen bei Koronarangiografien und -Interventionen. Kardiologe. 2015;9:295–302.
21. Schumacher B, Reichle B, Sommer P, Davé T, Levenson B, Reinecke H, et al. Kriterien für die Notwendigkeit und Dauer von Krankenhausbehandlung bei elektiven rhythmologischen Eingriffen. Kardiologe. 2017;11:209–218.
22. Latus J, Schwenger V, Schlieper G, Reinecke H, Hoyer J, Persson PB, et al. Kontrastmittelinduzierte akute Nierenschädigung – Konsensuspapier der Arbeitsgemeinschaft „Herz – Niere“ der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. und der Deutschen Gesellschaft für Nephrologie e.V. Kardiologe. 2020;14:494–504.

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Authorship
DGA Board: Erwin Blessing (Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Gefäßmedizin, Hamburg, Germany), Ludwig Caspary (Praxis für Innere Medizin/Angiologie/Phlebologie, Hannover, Germany), Wulf Ito (Herz- und Gefäßzentrum, Klinikverbund Allgäu, Kempten, Germany), Ralf Langhoff (Sankt Gertrauden-Krankenhaus GmbH, Gefäßzentrum Berlin, Berlin, Germany), Birgit Linnemann (Universitätsklinikum Regensburg, Gefäßzentrum Ostbayern, Regensburg, Germany), Nasser Malyar (Klinik für Kardiologie I, Universitätsklinikum Münster, Münster), Oliver J. Müller (Klinik für Innere Medizin III, Universitätsklinikum Schleswig-Holstein, Kiel), Tom Schilling (Harzklinikum Wernigerode, Innere Medizin und Gefäßzentrum, Wernigerode, Germany), Marcus Thieme (REGIOMED Klinikum Sonneberg, Innere Medizin und REGIOMED Gefäßzentrum, Sonneberg, Germany).

ESVM Board: Jill Belch (Institute of Cardiovascular Research, Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, Dundee, UK), Vinko Boc (Department of Vascular Diseases, University Clinical Centre, Ljubljana, Slovenia), Marianne Brodmann (Medical University Graz, Division of Angiology, Graz, Austria), Caitriona Canning (Vascular Medicine, Trinity College and James's Hospital, Dublin, Ireland), Patrick H Carpentier (Department of Vascular Medicine, Grenoble-Alpes University Hospital, Grenoble, France), Ali Chraim (Department of Vascular Surgery, Cedrus Vein and Vascular Clinic, Lviv Hospital, Lviv, Ukraine), Evangelos Dimakakos (Vascular Unit, 3rd Internal Medicine department, General Hospital, University of Athens School of Sotiria, Athens, Greece), Anders Gottsäter (Lund University, Department of Vascular Diseases, Skåne University Hospital, Sweden), Christian Heiss (University of Surrey, UK), Lucia Mazzolai (Lausanne University (UNIL), Switzerland), Angiology department), Juraj Madaric (Clinic of Angiology, National Cardiovascular Institute, Bratislava, Slovakia), Manuel Monreal (Hospital Universitari Germans Trias I Pujol, Badalona, Spain), Zsolt Pécsvárady (Vascular Center, Flor Ferenc Teaching Hospital, Kistarcsa, Hungary), Isabelle Quere (Médecine Vasculaire, Université de Montpellier, Montpellier, France), Dan Olinic (Iuliu Hatieganu University of Medicine and Pharmacy, Emergency Hospital, Medical Clinic no. 1, Cluj-Napoca, Romania), Karel Roztocil (Institute of Clinical and Experimental Medicine, Prague, Czech Republic), Agata Stanek (Department of Internal Diseases, Angiology and Physical Medicine, Medical University of Silesia, Bytom, Poland), Dragan Vasic (Clinical Centre of Serbia, Belgrade, Serbia), Adriana Visonà (Angiology Unit, Azienda ULSS 2 Marca Trevigiana, Castelfranco Veneto, Italy), Jean-Claude Wautrecht (Service de Pathologie Vasculaire, Hôpital Erasme, Université Libre de Bruxelles Brussels, Belgium).

Correspondence address
Dr. med. Marcus Thieme
REGIOMED Vascular Center and Department of Internal Medicine
Regiomed-Hospital GmbH
Neustadter Straße 61
96515 Sonneberg
Germany

marcus.thieme@regiomed-kliniken.de

Review

Best crossing of peripheral chronic total occlusions

A systematic algorithm and an interdisciplinary position statement

Grigorios Korosoglou[1], Andrej Schmidt[2], Michael Lichtenberg[3], Giovanni Torsello[4], Gerd Grözinger[5], Jihad Mustapha[6], Ramon L. Varcoe[7], Ito Wulf[8], Britta Heilmeier[9], Oliver J. Müller[10], Thomas Zeller[11], Erwin Blessing[12], and Ralf Langhoff[13]

[1] Cardiology and Vascular Medicine, GRN Hospital Weinheim, Germany
[2] Department of Interventional Angiology, University Hospital Leipzig, Germany
[3] Vascular Center, Klinikum Arnsberg, Germany
[4] Institute for Vascular Research, Franziskus Hospital, University Hospital Münster, Germany
[5] Department of Radiology, University of Tübingen, Germany
[6] Advanced Cardiac & Vascular Centers, Grand Rapids, Michigan, USA
[7] Department of Vascular Surgery, University of New South Wales, Sydney, Australia
[8] Cardiovascular Center Oberallgaeu-Kempten, Allgaeu Hospital Group, Immenstadt, Germany
[9] Gefäßpraxis im Tal, Munich, Germany
[10] Department of Internal Medicine III, German Centre for Cardiovascular Research, University Hospital Kiel, Partner Site Hamburg/Kiel/Lübeck, Germany
[11] Department of Interventional Angiology, University Hospital Freiburg/Bad Krozingen, Germany
[12] Department of Angiology, University Heart and Vascular Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[13] Brandenburg Medical School Theodor Fontane, Campus, Clinic Brandenburg, Berlin, Germany

Summary: Together with colleagues from different disciplines, including cardiologists, interventional radiologists and vascular surgeons, committee members of the of the German Society of Angiology (*Deutsche Gesellschaft für Angiologie* [*DGA*]), developed a novel algorithm for the endovascular treatment of peripheral chronic total occlusive lesions (CTOs). Our aim is to improve patient and limb related outcomes, by increasing the success rate of endovascular procedures. This can be achieved by adherence to the proposed crossing algorithm, aiding the standardization of endovascular procedures. The following steps are proposed: (i) APPLY Duplex sonography and if required 3D techniques such as computed tomography or magnetic resonance angiography. This will help you to select the optimal access site. (ii) EVALUATE the CTO cap morphology and distal vessel refilling sites during diagnostic angiography, which are potential targets for a retrograde access. (iii) START with antegrade wiring strategies including guidewire (GW) and support catheter technology. Use GW escalation strategies to penetrate the proximal cap of the CTO, which may usually be fibrotic and calcified. (iv) STOP the antegrade attempt depending on patient specific parameters and the presence of retrograde options, as evaluated by pre-procedural imaging and during angiography. (v) In case of FAILURE, consider advanced bidirectional techniques and reentry devices. (vi) In case of SUCCESS, externalize the GW and treat the CTO. Manage the retrograde access at the end of the endovascular procedure. (vii) STOP the procedure if no progress can be obtained within 3 hours, in case of specific complications or when reaching maximum contrast administration based on individual patient's renal function. Consider radiation exposure both for patients and operators. In this manuscript we systematically follow and explain each of the steps (i)–(vi) based on practical examples from our daily routine. We strongly believe that the integration of this algorithm in the daily practice of endovascular specialists, can improve vessel and patient specific outcomes.

Keywords: Peripheral chronic total occlusions (CTO), infrainguinal, antegrade/retrograde crossing, guidewires (GWs), re-entry catheter devices, duplex sonography, intravascular ultrasound, treatment algorithm, endovascular repair

Abbreviations

ACT: Activated clotting time
BTK: Below-the-knee
CFA: Common femoral artery
CLTI: Critical limb-threatening ischemia
CTA: Computed tomography angiography
CTO: Chronic total occlusion
CTOP: CTO based on plaque cap morphology
DCB: Drug coated balloon
DFA: Deep femoral artery
GW: Guidewire(s)
IVUS: Intravascular ultrasound
MRA: Magnetic resonance angiography
SFA: Superficial femoral artery

Introduction

Peripheral artery disease (PAD) is an endemic disease, which currently affects >200 million individuals worldwide [1, 2]. With an aging population however, the numbers are expected to further rise in future decades. Despite progress with pharmacologic treatments, such patients face high morbidity and mortality rates [1, 3]. Endovascular treatment for PAD is continuously evolving, with proven clinical benefits such as reduced limb pain in patients with claudication and limb salvage in patients with critical limb threatening ischemia (CLTI) [4, 5]. However, the recently published BEST-CLI study raised the issue that technical failure with endovascular procedures may trigger higher rates of adverse limb events, including major re-interventions and amputations during follow-up [6]. Therefore, standardization of endovascular procedures is crucial to further reduce failure rates and improve vessel and patient specific outcomes in patients treated endovascularly.

Together with colleagues from other disciplines, including cardiologists, interventional radiologists and vascular surgeons, committee members of the German Society of Angiology (*Deutsche Gesellschaft für Angiologie*, [*DGA*]) therefore developed a novel algorithm for the endovascular treatment of peripheral chronic total occlusive lesions (CTOs) [7]. Herein we aim to provide a practical approach to operators who are experienced with peripheral interventions but less experienced with CTO lesions, or operators experienced with large-vessel endovascular repair but not with infrainguinal CTOs. Achieving this goal by using practical case examples from our clinical practice, we believe that the integration of this algorithm in the daily practice will improve vessel and patient specific outcomes.

Selection of the primary access site and patient positioning

Careful preprocedural planning is crucial in order to have a successful procedure and avoid unnecessary complications [8, 9]. In addition, careful planning prior to the beginning of a procedure, considering the optimal primary access site and alternative crossing routes in case of an antegrade failure can help keeping low the radiation exposure and contrast agent administration.

Color-coded duplex ultrasound is a well-established diagnostic imaging tool not only for the detection of infrainguinal lesions but also for pre-procedural planning. Duplex is cost-effective, can be used at bedside and does not involve iodine contrast agent administration or ionizing radiation. Using duplex sonography, the level of the femoral bifurcation, the lesion length, the location of the occlusion and the severity of calcifications within the inflow and outflow of the target vessel, as well as the target plaque morphology, which vary based between homogenous vs heterogeneous and with or without thrombus can be assessed. In addition, Duplex sonography can help selecting the puncture access site and potential distal access sites in case of antegrade failure [10]. The latter can be performed by assessing the quality and measuring the diameter of tibial and peroneal arteries, which may act as distal access sites in case of an antegrade failure. In selected cases of complex anatomy, 3D imaging techniques, such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA) may be necessary for more precise pre-procedural planning. MRA has the advantage of not involving ionizing radiation for the patients, while CTA provides more precise visualization of lesion morphology and calcification.

Based on the lesion location and complexity, Duplex sonography, CTA or MRA help to determine the most effective primary access site, including cross-over, antegrade, retrograde or a trans-brachial access. Some practical examples of these 3 assess site options are listed below.

The cross-over approach

Figure 1 demonstrates a flush occlusion of the superficial femoral artery (SFA) i.e., an occlusion directly at the origin of the artery with a barely visible stump (A). Note that a short stump appears to be present after ipsilateral angulation of the C-arm (B). In such a case and in case of concomitant iliac lesions on the ipsilateral or contralateral site, needing attention, the cross-over approach represents the preferred strategy. In addition, the cross-over approach is preferable in obese patients, where an antegrade puncture may be associated with a higher chance for access site complications, such as a retroperitoneal hematoma or the formation of a pseudoaneurysm, especially if punctures are not performed under ultrasound guidance.

The antegrade approach

Figures 1C and 1D demonstrate the images of a patient with patent CFA and proximal and mid SFA and an occlusion of the distal SFA at the level of the Hunter's Canal (Figure 1C-D). In this case, and generally when a CTO is located >4-5cm distal to the origin of the SFA, the antegrade access,

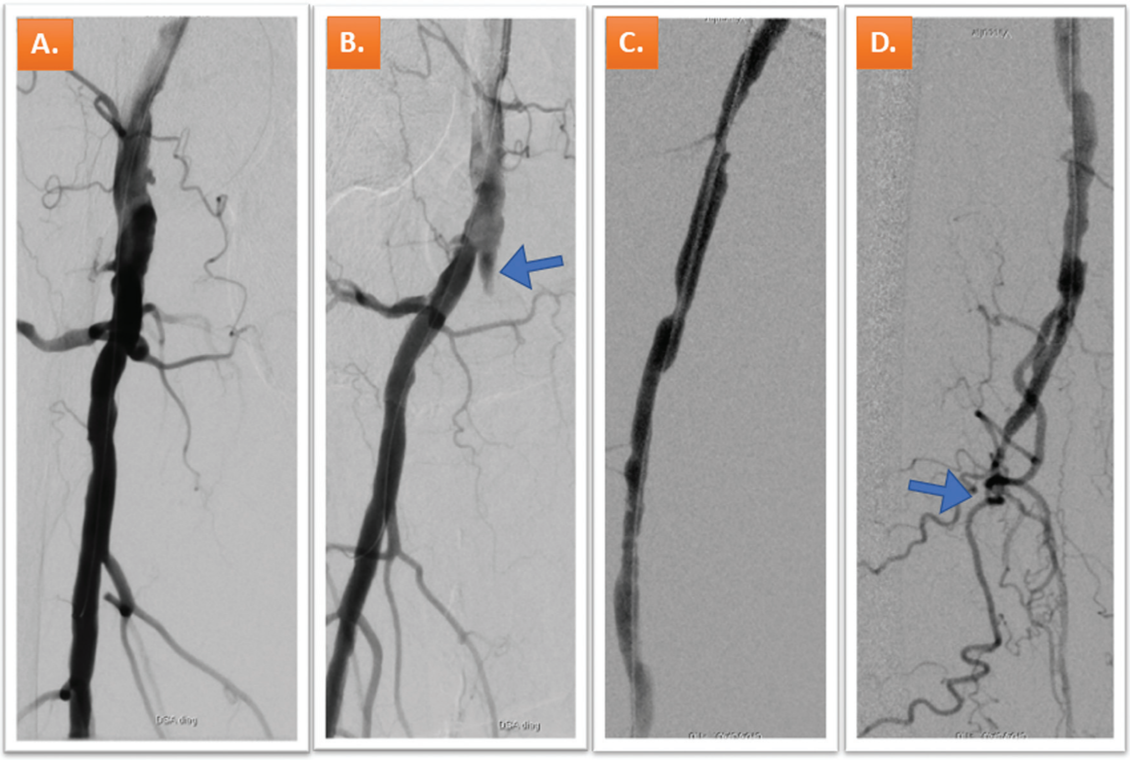

Figure 1. In case of flush SFA occlusion i.e., an occlusion directly at the origin of the artery with a barely visible stump, as seen in A, a cross-over approach is preferrable. Note that a short stump appears to be present after ipsilateral angulation of the C-arm (blue arrow in B). In patients with lesions or occlusions in the mid or distal SFA, on the other hand (C–D, blue arrow points to the occlusion in D), the antegrade access of the common femoral artery (CFA) is the favored option.

puncturing the common femoral artery (CFA) is the favored option. This access offers improved back-up for lesion crossing and prompt solution strategies for unanticipated complications, such as peripheral thromboembolism. Especially in case of thromboembolism in crural and pedal arteries, catheter aspiration can be performed more easily in case of an antegrade approach, whereas the limited shaft length of aspiration catheters, may make the aspiration of thrombotic debris using a cross-over approach difficult or impossible to reach. In addition, the antegrade approach offers additional advantages in CLTI patients, in case of concomitant lesions or occlusions of the ipsilateral below-the-knee (BTK) arteries, which in this case can be more easily tackled within the same session, compared to when using a cross-over approach. In some patients however, staged procedures targeting the inflow by a cross-over approach and then revascularizing BTK arteries within a second procedure may be preferable, especially in cases of frailty and chronic renal failure.

The transbrachial and transradial approaches

Transbrachial and transradial approaches were previously described as technically feasible and safe [11]. More recent studies, however, pointed to higher access site complication rates with the transbrachial approach, including bleeding or other complications requiring further treatment [12]. Generally, the transradial approach is considered safer in terms of access site complications. However, since with the transradial approach the distance to the CTO is even higher compared to the transbrachial strategy, restrictions, especially in terms of the shaft length of the balloon catheters and stents need to be taken into account [13]. In addition, since with both approaches passage of a GW and sheaths is required across the aortic arch, caution is necessary in the case of a thrombogenic aortic arch or a 'shaggy' aorta, where catheter manipulations may cause embolization and apoplex. Furthermore, data for the transradial access exist only for less complex infrainguinal lesions, whereas for complex and calcified CTOs the limited back-up provided with this approach may pose an additional limitation or make additional access sites during the procedure necessary [13]. This in turn, may cause additional complications since puncture of further access sites is performed after the administration of heparin, which is given at the beginning of the procedure.

Angiographic evaluation of the proximal and distal cap: the CTOP classification

Morphologically, CTOs consist of fibrotic and calcific tissue, which depending on their density and architecture may be decisive for the success or failure of endovascular procedures [14, 15]. It needs to be noted, that the exact length of the occlusion cannot be surely evaluated by angiography. Thus, contrast medium injected from the proximal sheath above the CTO flows through the collateral circulation, which then arrives to the main distal vessel. However, the contrast agent is unable to flow from

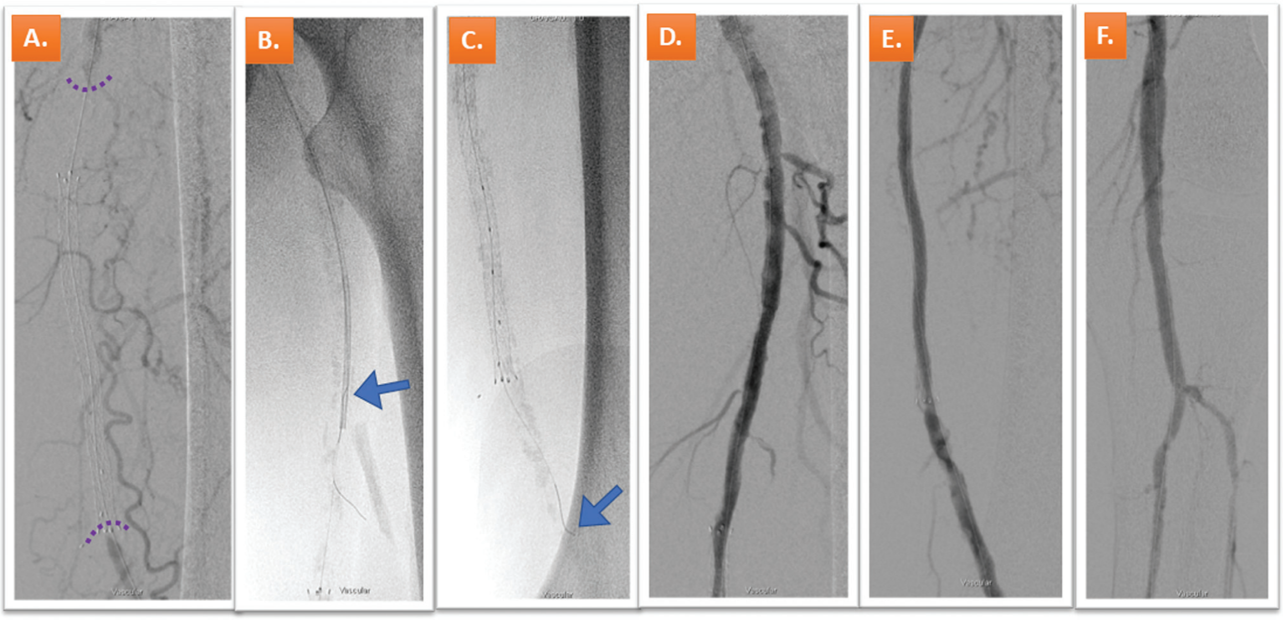

Figure 2. Type II lesion with a concave proximal cap and convex distal cap by the CTOP classification system (A). Due to this more complex plaque morphology, the antegrade wire passage was unsuccessful, so that a retrograde puncture of the occluded stent became necessary. After successful retrograde wire passage, externalization was performed using an antegrade guiding catheter (blue arrow in B) and the wire was reversed and passed antegrade through the occlusion using a 0.018′ support catheter (blue arrow in C). The final angiographic result after lesion preparation with a 6F Rotarex catheter and DCB angioplasty are provided in D-F.

the distal vessel upwards, even if the distal part of the angiographically defined CTO is patent. Therefore, the actual length of CTOs may be overestimated [16].

Some angiographic criteria, however, may predict the success or failure of endovascular management of complex CTO lesions. Thus, Saab et al. [17] focused on the morphology of the proximal and distal cap of CTO lesions, which is known as the plaque cap morphology (CTOP) classification system. Four scenarios have been described, depending on the convex or concave form of the proximal and distal cap of the CTO lesion and pose implications in terms of procedural success rates. With ascending CTOP types, alternative recanalization strategies become necessary due to an increasing risk of extraluminal crossing with inability to find the way back into the true lumen [18, 19]. Notably, the presence of flush occlusions and the origin of large caliber collaterals at the proximal cap are also factors, which may make an antegrade recanalization cumbersome or even impossible [20]. Furthermore, operators need to evaluate the presence of occluded stents within the CTO zone, since these may also be potential retrograde access sites [21]. Notably, the puncture of an occluded stent or of an occluded artery is associated with lower rates of bleeding complications.

Figure 2 demonstrates a Type II lesion with a concave proximal cap and convex distal cap (A). Due to this more complex plaque morphology, the proximal wire remains subintimal, so that a puncture of the occluded stent at its distal part becomes necessary. After successful retrograde wire passage through the occlusion, externalization is facilitated using an antegrade guiding catheter (B) and the wire is reversed and then passed antegrade through the occlusion using a 0.018′ support catheter (C). The final angiographic result after lesion preparation using a 6F Rotarex catheter and drug coated balloon (DCB) angioplasty are provided in D-F.

Antegrade wiring and GW escalation strategies

The antegrade passage is selected as the “first way to go” by most interventionalists. In this regard, most endovascular operators begin with a workhorse 0.035″ or 0.018″ GW for femoropopliteal and 0.018″ or 0.014″ GW for BTK lesions, respectively. In most cases, standard “working horses” GW are used in combination with support catheters to penetrate the CTO lesion. If such wires fail to cross, then escalating to dedicated CTO GW with higher tip load is the common practice. Since limited data exist to support a preference of specific GWs for specific lesions, GW selection and the choice of the support-catheter are mainly based on the operator’s experience [7].

GWs with relative low tip-load and polymer-sleeve can be successful for an intraluminal passage in non-severely calcified CTOs. Lower profile 0.018″ – or even 0.014″ – GWs may be preferable in very tight and calcified CTO segments. Nitinol- or hybrid-GWs on the other hand, have advantages in case of difficulties to drill the tip intraplaque forward and when the knuckle- or loop-technique becomes necessary. CTO-GWs can be used to penetrate intraluminally through shorter calcified segments, to penetrate the proximal or distal cap of the CTO lesion or to penetrate back into the true lumen distally. The tip-load of the GW needs to be chosen according to the severity of calcification

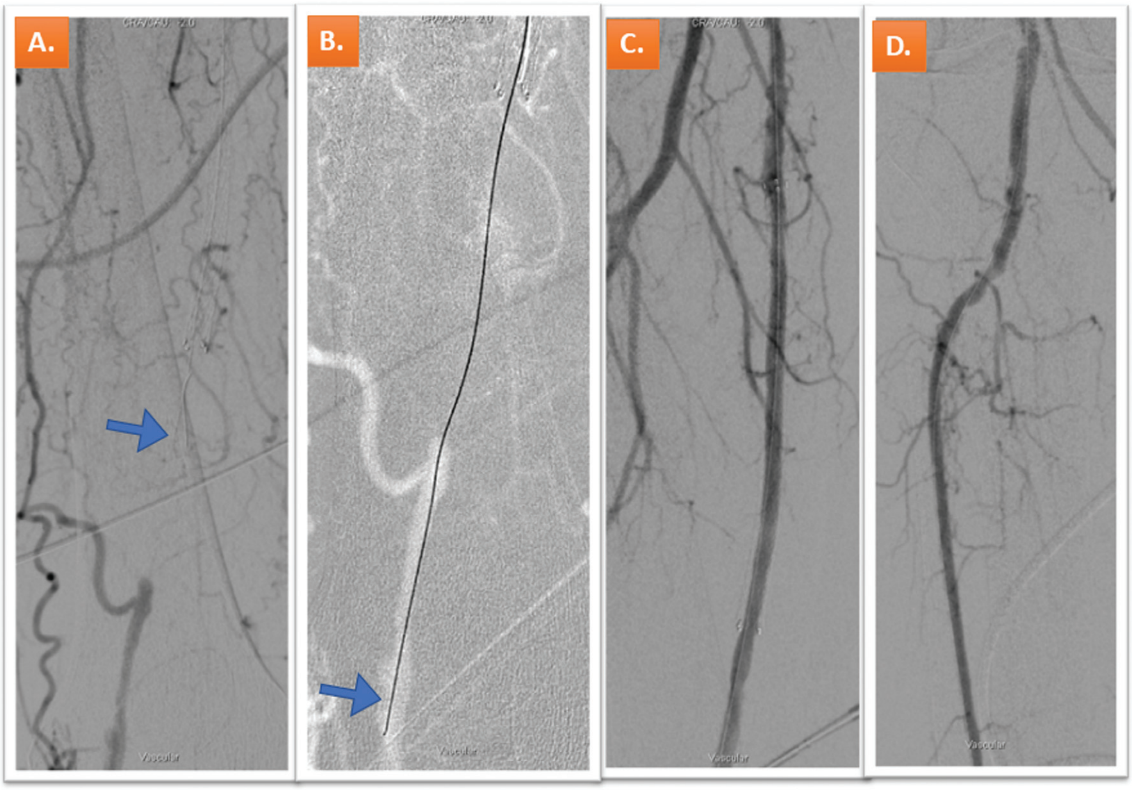

Figure 3. Stent occlusion at the level of the proximal and mid SFA. The working horse GW passes through the occluded stent but remains subintimal being unable to re-enter into the true lumen (blue arrow in A pointing to the tip of the antegrade GW). After exchanging to a dedicated 0.018′ CTO GW with a tapered micro-cone tip, over a support catheter, this GW achieves intraluminal passage and re-entry into the true lumen (blue arrow in B). The result after endovascular treatment from antegrade is shown in C-D.

and thickness of the cap. Higher tip loads provide a higher chance for penetration of the proximal cap, but this may come at the cost of GW extravasation and vessel perforation. Therefore, an escalation strategy may be justifiable, starting with lower tip load CTO wires, then proceeding with higher tip loads or changing from an antegrade to a retrograde strategy.

Figure 3 demonstrates a stent occlusion at the level of the proximal and mid SFA in a patient with claudication (RC 3). The working horse hybrid (steel/nitinol) GW creates a loop and can successfully pass through the occluded stent but remains subintimal being unable to re-enter into the true lumen of the artery (A). After exchanging to a dedicated 0.018′ CTO GW with a tapered micro-cone tip, over a support catheter, the latter achieves intraluminal passage and re-entry into the true lumen (B). The final result after debulking with a 6F Rotarex system and DCB angioplasty can be appreciated in C and D.

The question whether an intraluminal needs to be preferred over a subintimal GW passage, remains unanswered so far. Previous registries have shown diverse results in terms of success, complication rates and vessel patency [22, 23, 24]. In a recent study, the safety and efficacy of the subintimal approach were compared to intraluminal recanalization in patients with femoropopliteal CTO lesions [25]. IVUS was applied in all cases to verify subintimal versus intraluminal crossing of the CTO and propensity score matching analysis was performed to adjust for the intergroup differences. Hereby, the 2 recanalization techniques exhibited similar cumulative 1-year incidence of restenosis, whereas peri-procedural complications occurred more frequently in the subintimal arm [25]. However, randomized studies, which may address this question are not present in this area. The subintimal strategy may come with clear disadvantages if the dissection created proximally is extended into non-occluded or even healthy segments distally, which may unnecessarily compromise distal landing zones for future bypass grafts and exclude potential options for lesion preparation, such as atherectomy. Future studies are warranted to compare not only the acute success and complication rates but also long-term outcomes with subintimal versus intra-plaque recanalization strategies. Especially long and circumferentially calcified femoropopliteal CTOs may be impossible to pass fully intraluminally, even with bidirectional approaches. In such long and calcified complex occlusions, a subintimal recanalization strategy using the loop technique [26] may be justifiable since it may be the only chance to recanalize the occluded artery.

In addition, the role of IVUS is emerging in the field of peripheral vascular interventions. Thus, IVUS provides more accurate imaging detail compared to angiography, does not may additional contrast injections necessary, allows evaluation of the etiology of vessel occlusion and plaque morphology and differentiation between subintimal and intraluminal GW passage, which may influence the subsequent treatment strategies [27, 28].

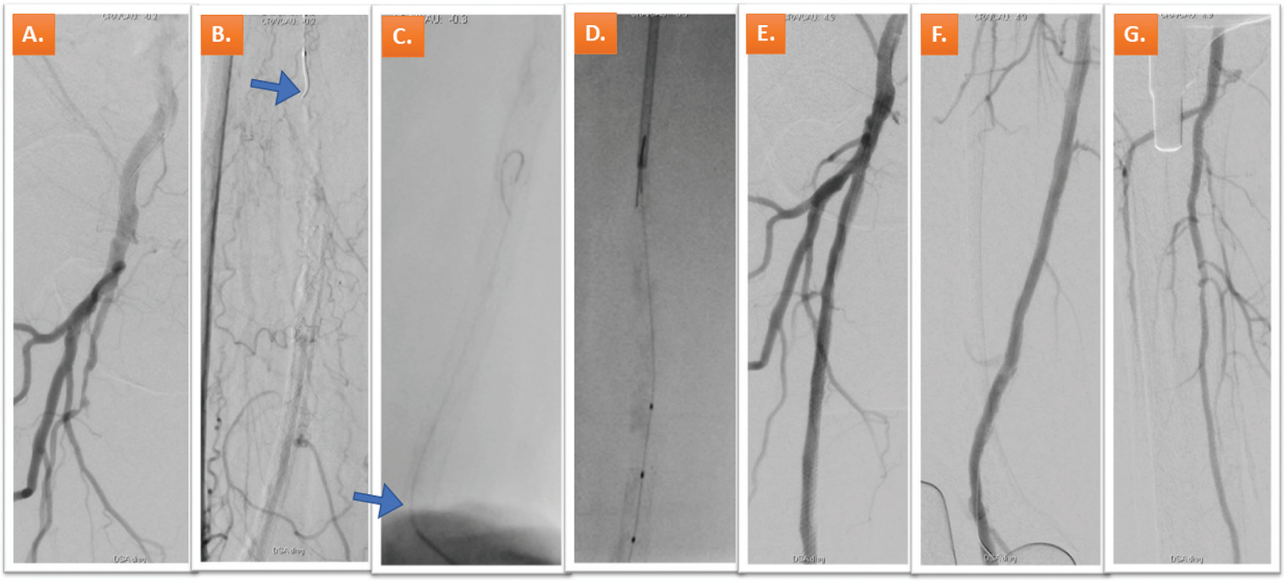

Figure 4. Severely calcified occlusion of the SFA (A) in a patient with prior intervention and stent placement. Due to the severe calcification, the antegrade GW remains in the subintimal space (blue arrow in B, pointing to the tip of the antegrade GW). Puncture of the stent is performed (blue arrow in C, pointing to the area of the retrograde puncture), allowing successful GW passage and subsequent externalization into a guiding catheter from antegrade (D). The final angiographic result is demonstrated in E-F.

Retrograde recanalization

After a failed antegrade crossing attempt, the retrograde approach or the use of a re-entry device from antegrade are usually considered as the next step. Especially in elderly and frail patients which represent the majority of the CLTI population, not being optimal candidates for open repair, the retrograde recanalization represents a limb and life-saving strategy [14, 15, 21, 29]. All operators treating complex CTOs need to be familiar with such recanalization techniques since endovascular failures are related to higher rates of adverse limb outcomes, such as amputation, death, and major re-interventions [6].

The distal access site

For femoropopliteal occlusions which do not exceed the adductor canal, the distal SFA or popliteal artery can be used as distal access sites [21]. The distal SFA runs under the sartorius muscle and can usually be punctured using a 7 cm or 9 cm long needle. In some cases, however, a 15 cm needle may be necessary, which can be guided through a 7cm 18G needle using a telescoping technique, thus facilitating more stable access through the sartorius muscle [30]. Prominent bilateral calcifications visible on fluoroscopy or occluded stents within the SFA may also serve as retrograde access sites [31]. Puncture of stents of calcified segments can be guided by fluoroscopy, whereas ultrasound is useful for the puncture of less calcified segments [29, 32]. Puncturing the popliteal artery from medially [33] or from anterolateral through the anterior muscular compartment also represent alternative options for occlusions which exceed to the P1 or P2 segment of the popliteal artery [34].

Figure 4 demonstrates an occlusion of the SFA (A) in a patient with CLTI (RC 4) and prior stent placement in the mid and distal SFA (B). Due to the severe calcification, the antegrade GW remains in the subintimal space (blue arrow in B). Puncture of the stent is performed from retrograde (C), resulting in successful GW passage and subsequent externalization into a guiding catheter from antegrade (D). The final angiographic result is depicted in E-G.

With lesions extending to the P3 segment of the popliteal artery or further distally, however, the distal SFA and the popliteal artery cannot be used as a retrograde access sites. In such cases, operators need to consider puncturing smaller diameter crural and pedal arteries for the retrograde access. In our experience the proximal anterior tibial artery represents a vessel segment, which can be punctured relatively easily using contrast assisted fluoroscopy. The anterior tibial artery can be accessed nearly at their entire length, whereas posterior tibial artery and the peroneal are typically punctured at their distal thirds [21].

Figure 5 demonstrates a patient with CLTI (RC 5) and occlusion of the distal SFA (blue arrow in A) and popliteal artery (B) with contrast refill at the level of the mid posterior tibial artery (C). Antegrade wiring with support catheter and wire escalation techniques lead to an extravasal route (blue arrow in D), as it can be verified by the route of the retrograde wire, inserted after puncture of the distal posterior tibial artery (red arrow in D). The retrograde GW is then externalized in a guiding catheter inserted from proximally (E). Contrast agent extravasation can be appreciated in F, at the area of the initial antegrade route. The final angiographic result after prolonged angioplasty and DCB treatment is shown in G and H.

Like the puncture of an occluded SFA, the puncture of occluded BTK arteries is also justifiable [35] since the risk

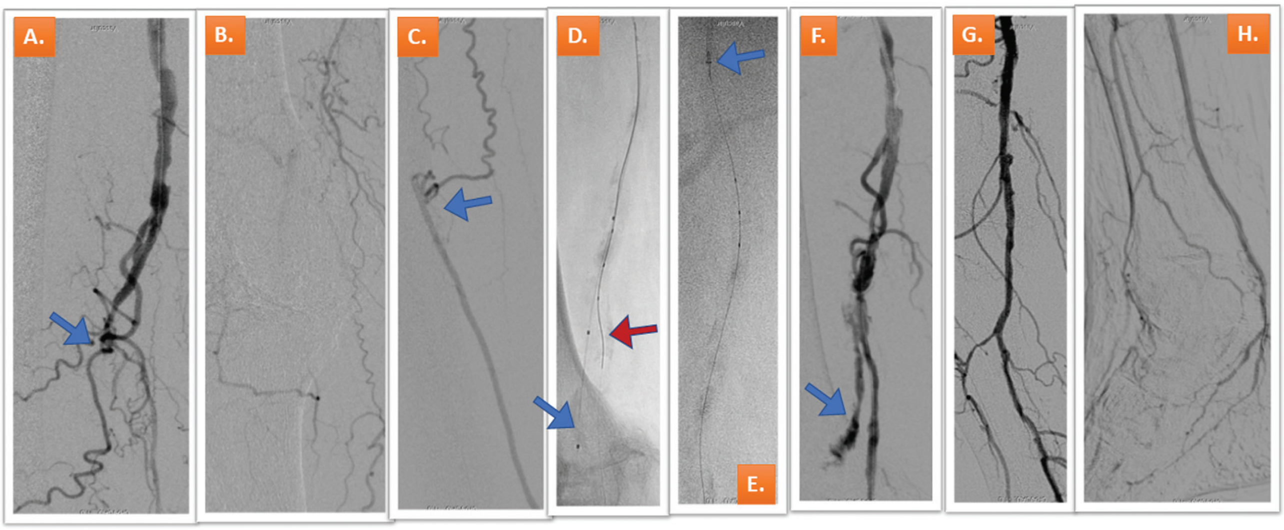

Figure 5. Patient with an occlusion of the distal SFA (blue arrow in A) and popliteal artery (B) with angiographic contrast refill at the level of the mid posterior tibial artery (blue arrow in C). Antegrade wiring lead to a false route (blue arrow in D), as it can be verified by the route followed by the retrograde wire (red arrow in D), which was inserted after puncture of the posterior tibial artery. Contrast agent extravasation can be appreciated in E, at the area of the initial false antegrade route. The final angiographic result after prolonged angioplasty and DCB treatment is demonstrated in G and H.

of bleeding complications is low when puncturing an occluded vessel segment. Furthermore, a pure retrograde approach has been proposed in patients, where an ipsilateral antegrade or contralateral cross-over access is challenging or not possible. This approach was described as the tibiopedal minimally invasive revascularization (TAMI) technique and has reasonable safety and technical success rates [36]. Careful ultrasound examination of pedal arteries prior to the procedure is necessary in such cases however, since small diameter or diseased pedal arteries may not be suitable as retrograde access sites for the TAMI technique.

After distal puncture, the type of retrograde access, including a sheath-less approach, a 2.9-F micro-puncture set, or standard 4-6F sheath needs to be chosen. Since larger diameter sheaths may be associated with higher complication rates, such as hematoma at the distal puncture site [14], most operators usually prefer to begin with a sheath-less approach first. If additional support is necessary to pass thought the CTO from retrograde, the insertion of a small diameter sheath can be considered. Based on recent studies, the technical success rate of the retrograde approach is high, varying between 93% and 96% [14, 29], whereas complication rates are low (0.6% dissections, 2.1% perforations, 1.3% local hematomas and 0.1% distal embolization [29]). Importantly, in CLTI patients, failed retrograde recanalization is associated with adverse limb outcomes in terms of significantly increased major amputation rates (8.5% versus 1.5%, $p<0.001$) [14].

GW selection and escalation strategies from retrograde

Due to the softer composition and thinner wall of the distal cap of the CTO, even complex and calcified lesions may be more easily crossed from retrograde [17, 37]. However, in some cases GW passage from retrograde may still be difficult, especially in CTOs, which have been existing for longer time. In such cases, after an unsuccessful intraluminal crossing attempt, GW escalation may also be the next step. In this regard, the use of angled microcatheters, GWs with higher tip load or a tapered micro-cone tip may be useful [38]. In case of unsuccessful intraluminal passage from retrograde, however, subintimal crossing of the GW from retrograde may be the next step, since a retrograde subintimal dissection may be corrected via the antegrade blood flow. In addition, intraluminal crossing can be challenging or impossible even from retrograde in case of long persisting and calcified CTOs.

Figure 6 demonstrates such a case of a severely calcified short occlusion of the SFA in a patient with CLTI (RC 5) (blue arrows in A), where the antegrade GW remains in the subintimal space due to severe calcification. After puncture of the proximal anterior tibial artery, support catheter is inserted without a sheath from retrograde (C). Since a regular GW cannot pass through the occlusion, a dedicated tapered micro-cone tip GW results in successful passage of the calcified occlusion from retrograde (blue arrow pointing to the tip of the retrograde wire in D). The angiographic result after wire externalization and balloon angioplasty is shown in E-G.

The plantar-loop technique

In BTK arteries, a special form of the retrograde recanalization of BTK arteries is the ‘plantar loop’ technique. With this technique, the GW is navigated through the plantar arch, coming from the dorsal pedal or across the lateral plantar artery. Using this technique, both the anterior and the posterior tibial artery can be recanalized using a single GW for the subsequent treatment. In case of insufficient support or trackability of the wire after passage through the planter loop, a retrograde puncture of the pedal artery

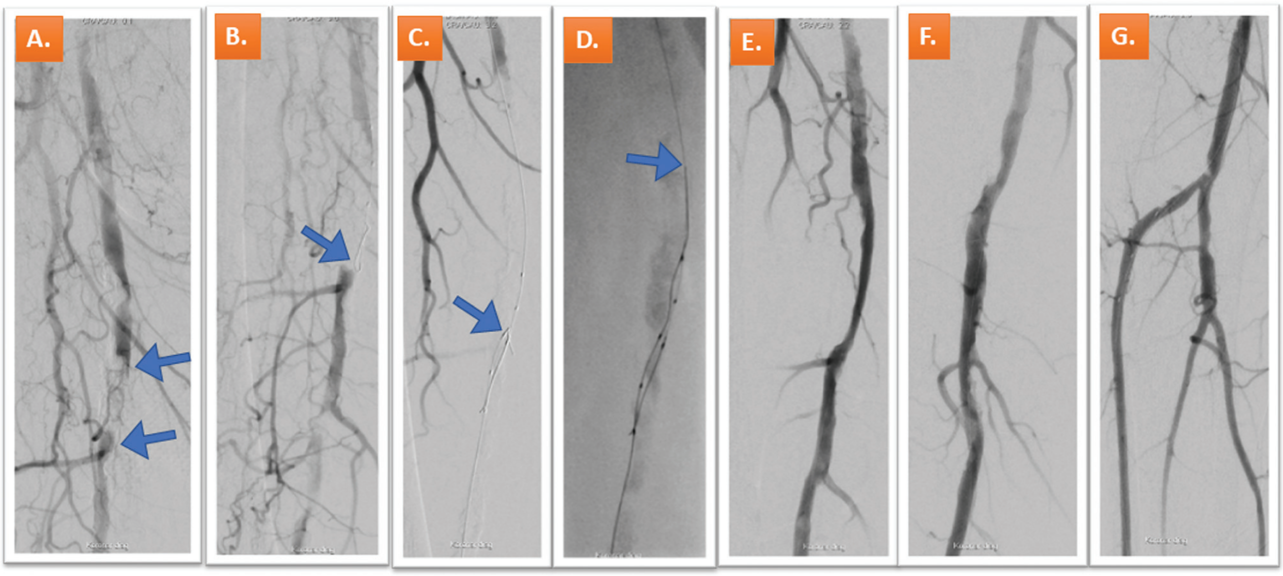

Figure 6. Severely calcified occlusion of the SFA (blue arrows in A), where the antegrade GW remains in the subintimal space (blue arrow in B). After puncture of the proximal anterior tibial artery (not shown), a sheath less support catheter is inserted from retrograde (C). However, the retrograde GW also cannot pass through the occlusion (blue arrow in C). Exchange to a tapered micro-cone tip GW, results in successful passage of the calcified occlusion from retrograde (blue arrow pointing to the tip of the retrograde wire in D). The angiographic result after wire externalization and balloon angioplasty is depicted in E-G.

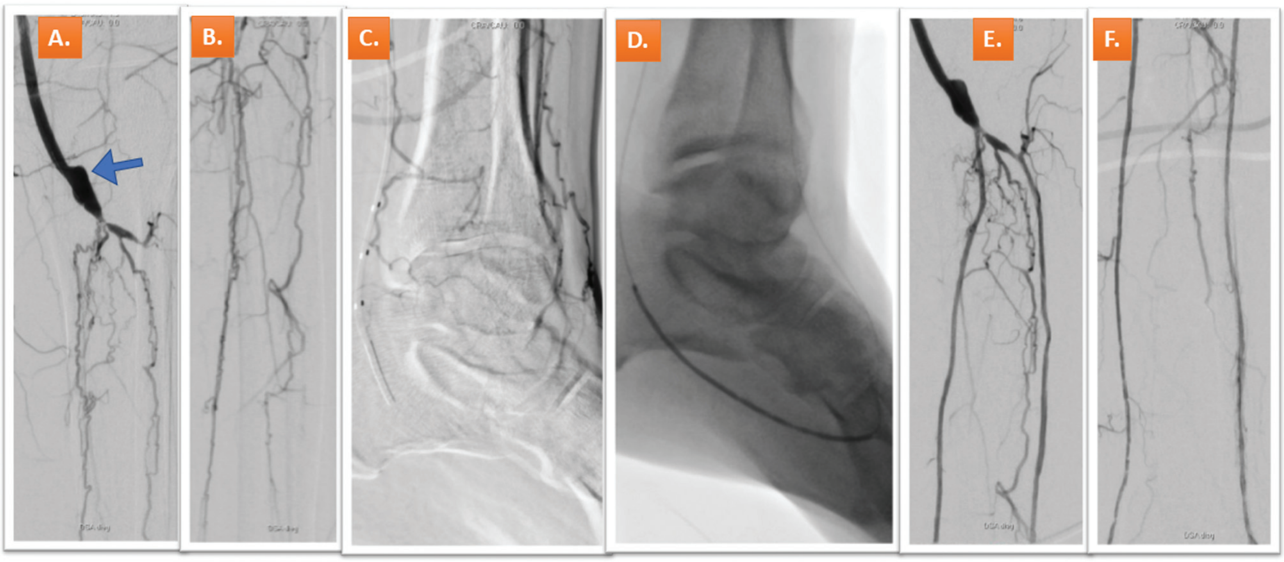

Figure 7. Occlusion of all 3 crural arteries in a patient with patent femoropopliteal venous graft (blue arrow in A). No native crurals or pedal vessels are present by angiography (B-C). After wiring of the posterior tibial artery, the wire is progressed across the pedal loop into the dorsal pedal and the anterior tibial artery. Subsequent prolonged angioplasty (D) leads to flow restoration in both the anterior and posterior tibial arteries (E-F).

guided by the GW, which is already ‘in place’ can be assessed. This technique has been reported to have high technical success rates of 85% and low complication rates and can be limb-saving especially in CLTI patients of RC5 and 6 [39].

Figure 7 demonstrates occlusion of all crural arteries in a patient with patent femoropopliteal venous graft (blue arrow in A), presenting with CLTI (RC 4). No native crurals or pedal vessels are observed distally by angiography (B-C). After wiring of the posterior tibial artery, the wire is progressed across the pedal loop into the dorsal pedal and the anterior tibial artery. Subsequent plain old balloon angioplasty (D) leads to flow restoration in both the anterior and posterior tibial arteries (E-F).

Alternative advanced strategies: Re-entry devices

Re-entry devices have been developed for re-entering into the intraluminal space after an unsuccessful subintimal recanalization attempt from either antegrade or retrograde. Such devices may help to avoid the extension of dissection

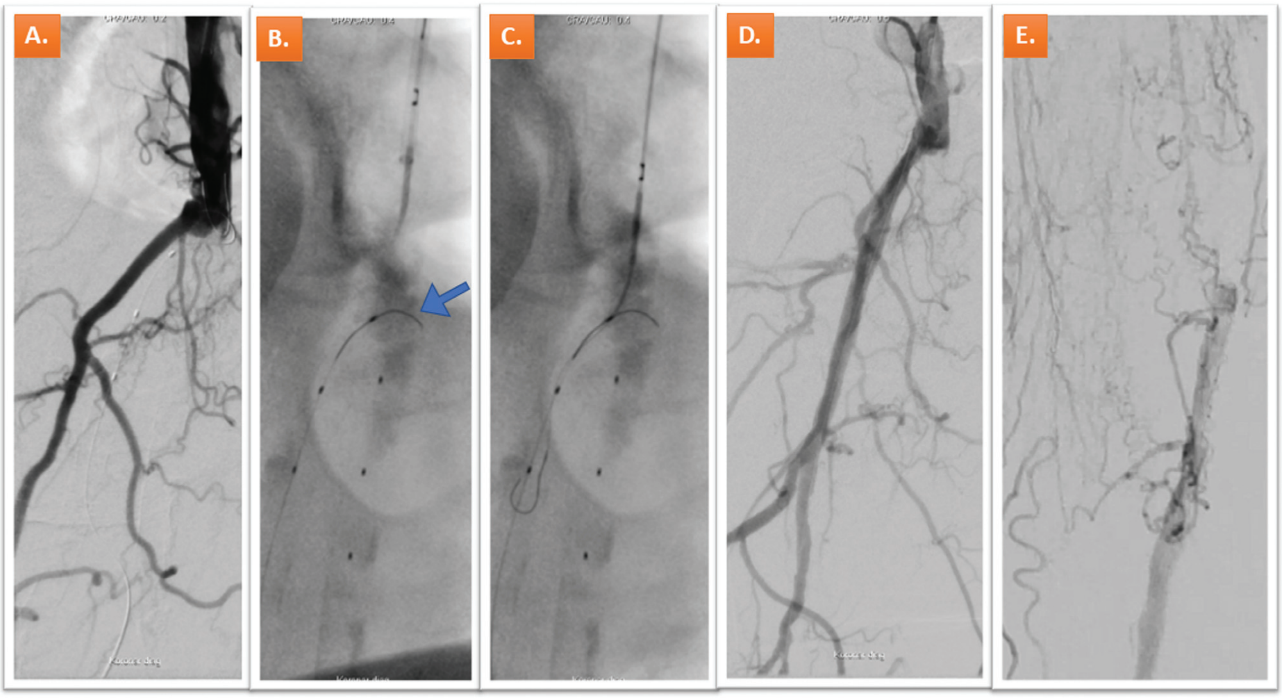

Figure 8. Patient with flush occlusion of both the SFA and the deep femoral artery (DFA) (A). Antegrade wiring was not successful for wiring of the SFA and DFA. Retrograde puncture of both arteries did not result in successful GW passage (blue arrow in B). Therefore, a low-profile GoBack™ re-entry catheter was inserted from antegrade, pointing to the retrograde support catheter around the proximal DFA (B-C). After puncture of the DFA by the needle of the catheter, the antegrade GW is guided intraplaque through the occlusion (C). The result, after reopening of the DFA is demonstrated in D-E.

planes from proximal to distally or vice versa and may also help reducing procedural time [40, 41]. However, additional costs are associated with such devices, which are not fully reimbursed in all countries. Their success rate is related to the experience of the operator and may also be limited by other factors, e.g., inability to advance the device over an aortic bifurcation with a steep angle via a crossover maneuver. In previous studies, failure rates up to 36% have therefore been described [42].

Based on lesion and patient specific characteristics and on the experience of the operators, re-entry devices may be selected for the recanalization of complex femoropopliteal lesions, especially by operators who are not yet sufficiently trained with retrograde techniques, or in case of less cooperative patients, where a retrograde puncture may be challenging.

In very complex cases however, the combination of retrograde access and the use of re-entry devices may be useful to tackle the CTO lesion. Thus, in cases, where the distal GW managed to pass the distal cap and parts of the CTO but is not able to penetrate through the proximal, the distal GW may aid as a target for a re-entry device from antegrade. In some cases, a balloon can be inserted from retrograde, which can be used as a target for the re-entry device from antegrade.

Figure 8 shows the images of a CLTI (RC 5) patient with flush occlusion of both the SFA and the deep femoral artery (DFA) (A). Antegrade wiring was not possible either in the SFA or in the DFA. In addition, retrograde puncture of both arteries also did not result in successful retrograde wire passage due to strong calcifications (blue arrow point to the tip of the retrograde wire after puncture of the DFA in B). Therefore, a low-profile GoBack catheters (Upstream Peripheral Technologies, Israel) re-entry catheter was inserted from antegrade, pointing to the retrograde support catheter around the proximal DFA (B-C). After direct puncture of the DFA by the needle of the catheter, the antegrade GW is guided intra-plaque through the occlusion (C). The result, after reopening of the DFA, with good collateral flow to the popliteal artery is shown in D-E.

In addition, retrograde insertion of re-entry devices was shown to be safe and effective for tackling challenging infrainguinal occlusions [30, 43]. Especially in patients after endarterectomy of the common femoral artery (CFA), re-entering into the true lumen through the retrograde access can be challenging. In such cases the retrograde insertion of a re-entry device, which is targeted toward the common femoral artery can result in technical success [44]. Caution is necessary in such complex cases, however, to avoid compromising the inflow of the DFA. In the interest of a low-profile approach, re-entry devices can also be inserted in a sheath-less manner if sufficient GW support is present.

This is demonstrated in Figure 9, where an occlusion of the SFA is noticed in a patient after CFA endarterectomy (A). After successful puncture of an occluded stent in the mid SFA (B), a low-profile re-entry catheter is progressed from retrograde up to the level of the CFA (C). After rotation of the re-entry catheter to the direction of the CFA, the artery is punctured, resulting in successful GW passage from retrograde (D). The result can be appreciated after GW externalization and endovascular treatment from antegrade (E).

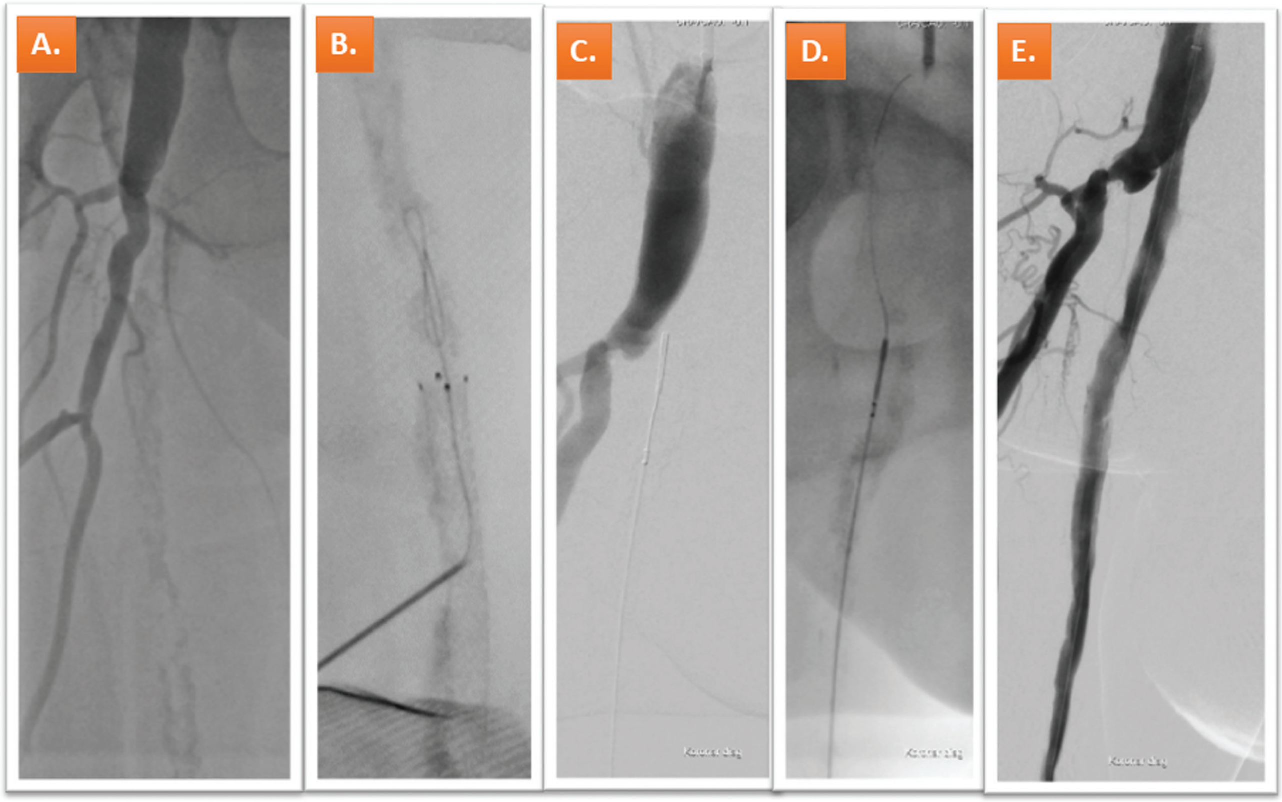

Figure 9. Occlusion of the SFA in a patient after CFA endarterectomy (A). After puncture of an occluded stent in the mid SFA (B), a low-profile re-entry catheter is progressed from retrograde up to the level of the CFA (C). After rotation of the re-entry catheter to the direction of the CFA, the artery is punctured, resulting in successful GW passage (D). The result is demonstrated after GW externalization and endovascular treatment from antegrade (E).

In some cases, even with re-entry devices, GW passage may not be successful. In such cases, a balloon can be positioned as a target for the needle of a re-entry device. This may facilitate successful wire crossing, as reported previously in a relatively small number of patients [45]. The recently launched GoBack device, which is available in 4F and 2.9F can be introduced via a sheath or in a sheath-less manner [46]. Due to its lower profile, the GoBack catheter can be advanced from either ante- or retrograde to puncture into a balloon, positioned at the opposite side. Generally, points of severe calcification may be challenging if chosen as re-entry points. In summary, re-entry devices may be used as an alternative or additionally to retrograde or bidirectional recanalization techniques to enable GW passage back into the intraluminal space. Such advanced options can help to further enhance technical success rates in complex occlusions and may provide solutions for otherwise 'no-option' patients.

Management of the distal access site and of potential complications

After successful retrograde GW passage, the GW is then externalized through the proximal sheath, resulting through-and-through access. This access provides high support for the subsequent endovascular treatment. In cases where the distal GW cannot be maneuvered due to high friction or is unable to enter the proximal sheath, balloon angioplasty via the retrograde GW, either sheath-less or using a low-profile sheath may be an alternative option. After balloon dilatation from retrograde, a working horse GW may be able to be advanced from proximal, aiding subsequent endovascular treatment. However, such maneuvers need to be performed with caution since antegrade wires may still tend to enter subintimal planes from proximal, even after pre-dilatation of the lesion from distally.

At the end of the endovascular procedure, a balloon is usually inserted across the distal puncture area to provide internal hemostasis. Alternatively, hemostasis can be achieved by external manual compression. In very rare cases, if hemostasis cannot be achieved at the distal puncture site even after prolonged manual compression or internal balloon inflation, the application of a covered stent may represent a bail-out treatment option. However, limited data are available on the long-term patency of crural vessels after such a covered stent placement.

In case of failed crossing after application of antegrade, retrograde and advanced techniques, accepting procedural failure is also important to avoid high radiation and contrast agent exposure and patient and vessel specific complications. Procedural duration >3 hours and contrast volume more than 3 times the estimated glomerular filtration rate are indicators for stopping the endovascular procedure, especially if wire passage is not achieved at this time point.

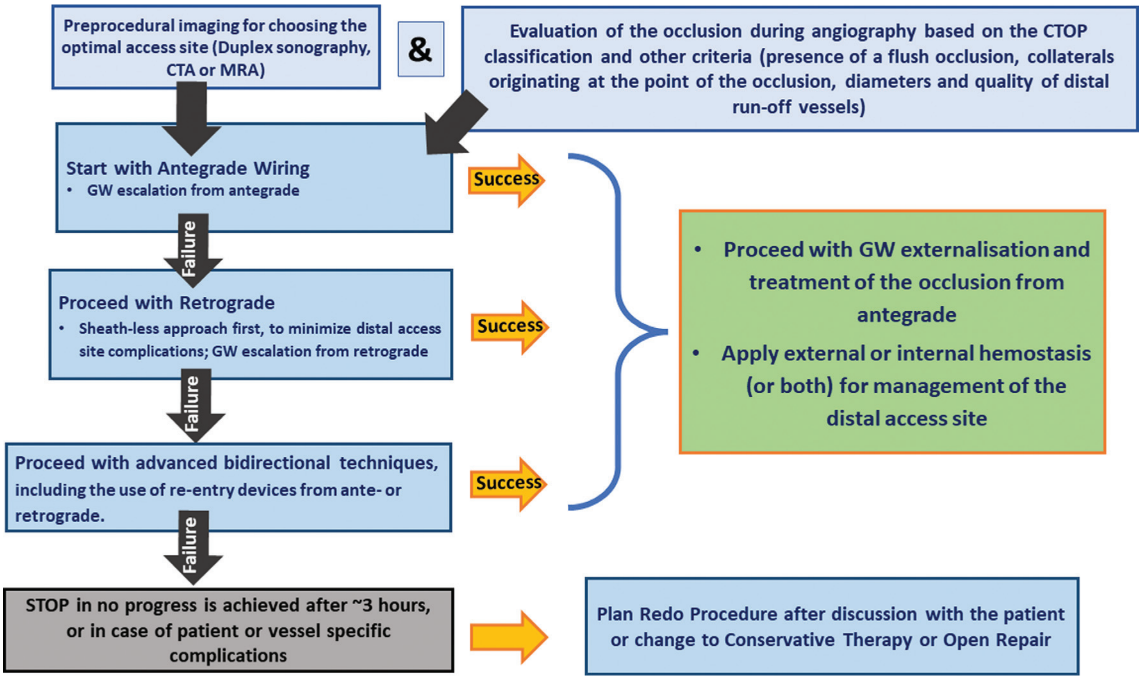

Figure 10. Our CTO crossing algorithm encompasses antegrade, retrograde, bidirectional, and advanced techniques for the endovascular revascularization of complex CTO lesions in peripheral arteries. Steps and considerations encompass pre-procedural planning, angiographic evaluation of proximal and distal cap by the CTOP classification system, ante- and retrograde recanalization techniques, including wire escalation strategies, re-entry devices and management of potential complications.

On the other hand, with such time-consuming procedures, the frequent assessment of the activated clotting time (ACT) needs to be kept in mind. Typically, 5.000 IU of unfractionated heparin is administrated at the beginning of the procedure and the ACT needs to be controlled regularly every 30 minutes. An ACT between 200-250s is targeted during the procedure, to minimize the risk for both thromboembolic and bleeding complications [47]. Acceptance of failure may be much easier to accept in patients with lifestyle limiting claudication compared to CLTI patients.

Importance of the standardization of endovascular procedures considering the BEST-CLI trial

The first results of the BEST-CLI (Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia) study were recently published [6]. This trial represents an important effort to obtain randomized data, comparing 2 major revascularization treatment options in patients with CLTI, i.e., surgical versus endovascular revascularization. In cohort 1 of this study (1,434 patients with a good quality single-segment-saphenous vein), surgery was associated with lower major surgical reintervention, above-the-ankle amputation and death rates (42.6% versus 57.4%), whereas in cohort 2 (396 patients requiring alternative conduits) outcomes were similar between endovascular revascularization and open repair (42.8% versus 47.7%) [6]. Subjects were enrolled over 62 months with a median follow-up over 2.7 years.

The main conclusion of the authors was the favorable outcomes of patients who had an adequate great saphenous vein for surgical revascularization in cohort 1 compared to those who underwent endovascular treatment, while analysis of the data, especially in terms of quality of life is still ongoing. However, these data need to be interpreted with caution. Technical success rates with endovascular treatment were lower than expected from experienced operators (85% and 80%, in cohorts 1 and 2, respectively), which deserves further analysis since this high failure rate substantially triggered subsequent re-interventions and above-the-ankle amputations, influencing the primary endpoint of the study. The high rate of endovascular failures indicates that advanced crossing and recanalization techniques, as reported previously [14, 21, 29] and reviewed herein, may not have been used on a regular basis and in all centers which enrolled patients for the trial. This stresses the importance of standardization and harmonization of endovascular procedures, which is expected to increase success rates and hereby improve patient and limb related outcomes.

Conclusions

Our CTO crossing algorithm encompasses antegrade, retrograde, bidirectional, and advanced techniques, including re-entry devices for the endovascular repair of complex peripheral CTO lesions. The corresponding steps, which also include preprocedural planning, angiographic evaluation of the CTO and management of the distal access sites and of potential complications are summarized in Figure 10 and can be easily implemented in daily clinical practice.

The implementation of our algorithm as part of clinical routine will be useful for further increasing the success rates, avoiding peri-procedural complications, and improving limb and patient related outcomes. In addition, continuous education, and collaboration between experts from different disciplines is warranted.

References

1. Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. Vasa. 2019;48(S102):1–79.
2. Gallino A, Aboyans V, Diehm C, Cosentino F, Stricker H, Falk E, et al. Non-coronary atherosclerosis. Eur Heart J. 2014;35(17):1112–9.
3. Giusca S, Hagstotz S, Lichtenberg M, Heinrich U, Eisenbach C, Andrassy M, et al. Phoenix atherectomy for patients with peripheral artery disease. EuroIntervention. 2022;18(5):e432–e42.
4. Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. JAMA. 2015;314(18):1936–44.
5. Kreutzburg T, Peters F, Riess HC, Hischke S, Marschall U, Kriston L, et al. Editor's Choice – Comorbidity patterns among patients with peripheral arterial occlusive disease in Germany: a trend analysis of health insurance claims data. Eur J Vasc Endovasc Surg. 2020;59(1):59–66.
6. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med. 2022;387(25):2305–16.
7. Korosoglou G, Schmidt A, Lichtenberg M, Torsello G, Grozinger G, Mustapha J, et al. Crossing algorithm for infrainguinal chronic total occlusions: an interdisciplinary expert opinion statement. JACC Cardiovasc Interv. 2023;16(3):317–31.
8. Boc V, Boc A, Zdesar U, Blinc A. Patients' radiation doses during percutaneous endovascular procedures in arteries of the lower limbs. Vasa. 2019;48(2):167–74.
9. Prasad A, Hughston H, Michalek J, Trevino A, Gupta K, Martinez JP, et al. Acute kidney injury in patients undergoing endovascular therapy for critical limb ischemia. Catheter Cardiovasc Interv. 2019;94(4):636–41.
10. Mustapha JA, Diaz-Sandoval LJ, Jaff MR, Adams G, Beasley R, Finton S, et al. Ultrasound-guided arterial access: outcomes among patients with peripheral artery disease and critical limb ischemia undergoing peripheral interventions. J Invasive Cardiol. 2016;28(6):259–64.
11. Basche S, Eger C, Aschenbach R. Transbrachial angiography: an effective and safe approach. Vasa. 2004;33(4):231–4.
12. Mantripragada K, Abadi K, Echeverry N, Shah S, Snelling B. Transbrachial access site complications in endovascular interventions: a systematic review of the literature. Cureus. 2022;14(6):e25894.
13. Sher A, Posham R, Vouyouka A, Patel R, Lookstein R, Faries PL, et al. Safety and feasibility of transradial infrainguinal peripheral arterial disease interventions. J Vasc Surg. 2020;72(4):1237–46 e1.
14. Korosoglou G, Schmidt A, Stavroulakis K, Pollert D, Giusca S, Lichtenberg M, et al. Retrograde access for the recanalization of lower-limb occlusive lesions: a German experience report in 1,516 consecutive patients. JACC Cardiovasc Interv. 2022;15(3):348–51.
15. Schmidt A, Bakker OJ, Bausback Y, Scheinert D. The tibiopedal retrograde vascular access for challenging popliteal and below-the-knee chronic total occlusions: literature review and description of the technique. J Cardiovasc Surg. 2017;58(3):371–82.
16. Mustapha JA, Diaz-Sandoval LJ, Saab F. Infrapopliteal calcification patterns in critical limb ischemia: diagnostic, pathologic and therapeutic implications in the search for the endovascular holy grail. J Cardiovasc Surg. 2017;58(3):383–401.
17. Saab F, Jaff MR, Diaz-Sandoval LJ, Engen GD, McGoff TN, Adams G, et al. Chronic total occlusion crossing approach based on plaque cap morphology: the ctop classification. J Endovasc Ther. 2018;25(3):284–91.
18. Turkyilmaz S, Kavala AA. The relationship between plaque cap morphology and access technique in lower extremity chronic total occlusion. Vascular. 2019;27(2):135–43.
19. Bernardini G, Bisdas T, Argyriou A, Saab F, Torsello G, Tsilimparis N, et al. Risk factor analysis for crossing failure in primary antegrade wire-catheter approach for femoropopliteal chronic total occlusions. J Endovasc Ther. 2022;15266028221083456.
20. Giusca S, Lichtenberg M, Hagstotz S, Eisenbach C, Katus HA, Erbel C, et al. Comparison of ante-versus retrograde access for the endovascular treatment of long and calcified, de novo femoropopliteal occlusive lesions. Heart Vessels. 2020;35(3):346–59.
21. Schmidt A, Bausback Y, Piorkowski M, Wittig T, Banning-Eichenseer U, Thiele H, et al. Retrograde Tibioperoneal Access for Complex Infrainguinal Occlusions: Short- and Long-Term Outcomes of 554 Endovascular Interventions. JACC Cardiovasc Interv. 2019;12(17):1714–26.
22. Kondapalli A, Jeon-Slaughter H, Lu H, Xu H, Khalili H, Prasad A, et al. Comparative assessment of patient outcomes with intraluminal or subintimal crossing of infrainguinal peripheral artery chronic total occlusions. Vasc Med. 2018;23(1):39–45.
23. Kim K, Ko YG, Ahn CM, Min PK, Lee JH, Yoon CH, et al. Clinical outcomes of subintimal vs. intraluminal revascularization approaches for long femoropopliteal occlusions in a Korean multicenter retrospective registry cohort. Circ J. 2018;82(7):1900–7.
24. Soga Y, Iida O, Suzuki K, Hirano K, Kawasaki D, Shintani Y, et al. Initial and 3-year results after subintimal versus intraluminal approach for long femoropopliteal occlusion treated with a self-expandable nitinol stent. J Vasc Surg. 2013;58(6):1547–55.
25. Tomoi Y, Takahara M, Kuramitsu S, Soga Y, Iida O, Fujihara M, et al. Subintimal versus intraluminal approach for femoropopliteal chronic total occlusions treated with intravascular ultrasound guidance. J Am Heart Assoc. 2021;10(20):e021903.
26. Kawarada O, Sakamoto S, Harada K, Ishihara M, Yasuda S, Ogawa H. Contemporary crossing techniques for infrapopliteal chronic total occlusions. J Endovasc Ther. 2014;21(2):266–80.
27. Secemsky EA, Mosarla RC, Rosenfield K, Kohi M, Lichtenberg M, Meissner M, et al. Appropriate use of intravascular ultrasound during arterial and venous lower extremity interventions. JACC Cardiovasc Interv. 2022;15(15):1558–68.
28. Secemsky EA, Parikh SA, Kohi M, Lichtenberg M, Meissner M, Varcoe R, et al. Intravascular ultrasound guidance for lower extremity arterial and venous interventions. EuroIntervention. 2022;18(7):598–608.
29. Giannopoulos S, Palena LM, Armstrong EJ. Technical success and complication rates of retrograde arterial access for endovascular therapy for critical limb ischaemia: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2021;61(2):270–9.
30. Schmidt A, Bausback Y, Piorkowski M, Werner M, Braunlich S, Ulrich M, et al. Retrograde recanalization technique for use after failed antegrade angioplasty in chronic femoral artery occlusions. J Endovasc Ther. 2012;19(1):23–9.
31. Palena LM, Manzi M. Direct stent puncture technique for intraluminal stent recanalization in the superficial femoral and popliteal arteries in-stent occlusion: outcomes from a prospective clinical analysis of diabetics with critical limb ischemia. Cardiovasc Revasc Med. 2013;14(4):203–6.

32. Kawasaki D, Yamada T, Fukunaga M. Feasibility and safety of the direct occluded vessel puncture technique as a new access site for complex peripheral artery occlusive disease. J Atheroscler Thromb. 2021;28(4):349–55.
33. Fanelli F, Lucatelli P, Allegritti M, Corona M, Rossi P, Passariello R. Retrograde popliteal access in the supine patient for recanalization of the superficial femoral artery: initial results. J Endovasc Ther. 2011;18(4):503–9.
34. Silvestro M, Palena LM, Manzi M, Gomez-Jabalera E, Vishwanath D, Casini A, et al. Anterolateral retrograde access to the distal popliteal artery and to the tibioperoneal trunk for recanalization of femoropopliteal chronic total occlusions. J Vasc Surg. 2018;68(6):1824–32.
35. Uyanik SA, Oguslu U, Yilmaz B, Cevik H, Atli E, Gumus B. Retrograde pedal access via occluded arteries in endovascular treatment of critical limb ischemia. J Vasc Interv Radiol. 2021;32(2):164–72.
36. Mustapha JA, Saab F, McGoff TN, Adams G, Mullins JR, Al-Dadah A, et al. Tibiopedal arterial minimally invasive retrograde revascularization (TAMI) in patients with peripheral arterial disease and critical limb ischemia. On behalf of the Peripheral Registry of Endovascular Clinical Outcomes (PRIME). Catheter Cardiovasc Interv. 2020;95(3):447–54.
37. Thind A, Strauss B, Teitelbaum A, Karshafian R, Ladouceur M, Whyne C, et al. A novel method for the measurement of proximal fibrous cap puncture force in chronic total occlusions: the effect of increasing age. EuroIntervention. 2011; 6(8):997–1002.
38. Nikolakopoulos I, Choi JW, Alaswad K, Khatri JJ, Krestyaninov O, Khelimskii D, et al. Equipment utilization in chronic total occlusion percutaneous coronary interventions: Insights from the PROGRESS-CTO registry. Catheter Cardiovasc Interv. 2021;97(4):658–67.
39. Manzi M, Palena LM. Treating calf and pedal vessel disease: the extremes of intervention. Semin Intervent Radiol. 2014; 31(4):313–9.
40. Kitrou P, Parthipun A, Diamantopoulos A, Paraskevopoulos I, Karunanithy N, Katsanos K. Targeted true lumen re-entry with the outback catheter: accuracy, success, and complications in 100 peripheral chronic total occlusions and systematic review of the literature. J Endovasc Ther. 2015;22(4):538–45.
41. Kawasaki D, Fukunaga M, Nakata T, Kato M, Ohkubo N. Comparison of the OUTBACK((R)) elite reentry catheter and the bi-directional approach after failed antegrade approach for femoro-popliteal occlusive disease. J Atheroscler Thromb. 2017;24(12):1242–8.
42. Shin SH, Baril D, Chaer R, Rhee R, Makaroun M, Marone L. Limitations of the Outback LTD re-entry device in femoropopliteal chronic total occlusions. J Vasc Surg. 2011;53(5): 1260–4.
43. Patrone L, Stehno O. Retrograde insertion of the outback reentry device from a tibial artery for complex infrainguinal recanalization. CVIR Endovasc. 2019;2(1):47.
44. Patrone L, Dharmarajah B, Korosoglou G, Theivacumar S, Antaredja M, Oberacker R, et al. Retrograde use of the Outback re-entry catheter in complex infrainguinal arterial recanalizations. J Vasc Surg. 2022;75(1):177–85.e1.
45. Tai Z, Lee A. Reentry-catheter assisted SAFARI technique. J Invasive Cardiol. 2015;27(7):e146–e152.
46. Bakker O, Bausback Y, Wittig T, Branzan D, Steiner S, Fischer A, et al. First experience with the goback-catheter for successful crossing of complex chronic total occlusions in lower limb arteries. J Endovasc Ther. 2022;29(5):798–807.
47. Doganer O, Wiersema AM, Pierie M, Blankensteijn JD, Yeung KK, Jongkind V. More effective anticoagulation during non-cardiac arterial procedures using activated clotting time guided heparin administration. Ann Vasc Surg. 2021;76:378–88.

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Conflict of Interest

AS is consultant for Abbott, Cook Medical, Reflow Medical and Upstream Peripheral. *EB* received speaker honoraria from Cardinal Health, Abbott Vascular, Philips, Biotronik, Boston Scientific Corp., Medtronic, Terumo and Shockwave. *GG* received speaker honoraria from Abbot, Biotronik, Cordis and Siemens. *GK* received speaker honoraria from Philips, Boston scientific, BALT Germany GmbH and BARD Peripheral Vascular Inc., and institutional grants from Philips, Siemens and Bard Peripheral Vascular Inc. *GT* received research funding and speaker honoraria from Boston Scientific, WL Gore, Cook, and Medtronic. *JM* consultant for Angiodynamics, Avinger, Bard Peripheral Vascular Inc., Cardiovascular Systems Inc., Medtronic, PQ Bypass (Endologix), Philips and Terumo. *ML: Honoraria received from:* Abbott Vascular, BD Bard, Medalliance, Biotronik, Boston Scientific Corp., Cook Medical, Medtronic, Philips, Shockwave, Veryan, Limflow, Biotronik, Cordis CSI, Penumbra, Cardionovum; *Consulted for:* CSI, Gore & Associates, Medtronic, Veryan, Philips-Intact Vascular, Shockwave, Bayer, Vesper Medical, Cagent Vascular, Cordis, Medalliance, Reflow Medical, Bolt Medical; *Institutional Grants for research, clinical trial, or drug studies received from:* Bard Peripheral Vascular, Veryan, Biotronik, Philips, Terumo, Med Alliance, Intact Vascular, Surmodics, Reflow Medical, Cardionovum. *OM* received honoraria from Bayer, Bristol-Myers-Squib, Daiichi-Sankyo, Novartis, Pfizer and Servier and consultant fees from Bayer; *Institutional grants for clinical trials* from Anthos Therapeutics, Novartis and Rheacell. *RL* has lectured and received research grants from B. Braun. *RV* received modest consultant fees from Abbott Vascular, Boston Scientific, Philips, W.L. Gore, BD Bard, Medtronic, Nectero, Intervene and Surmodics. *TZ: Honoraria received from:* Abbott Vascular, Biotronik, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, Shockwave, Veryan; *Consulted for:* Boston Scientific Corp., CSI, Gore & Associates, Medtronic, Veryan, Philips-Intact Vascular, Shockwave, Bayer, Vesper Medical, VentureMed, ANT; *Institutional Grants for research, clinical trial, or drug studies received from:* Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Gore & Associates, Medtronic, Philips, Terumo, TriReme, Shockwave, Med Alliance, Intact Vascular, B. Braun; CSI, Boston Scientific, University of Jena, Pluristem, PQ Bypass, Surmodics, Reflow Medical, Ablative Solutions

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ORCID
Grigorios Korosoglou
https://orcid.org/0000-0002-6038-2253
Andrej Schmidt
https://orcid.org/0000-0003-4786-3957
Michael Lichtenberg
https://orcid.org/0000-0003-2647-9876
Oliver J. Müller
https://orcid.org/0000-0001-8223-2638
Thomas Zeller
https://orcid.org/0000-0003-2704-3871
Erwin Blessing
https://orcid.org/0000-0003-0205-9084
Ralf Langhoff
https://orcid.org/0000-0003-0455-5081

Correspondence address
Prof. Dr. Grigorios Korosoglou
GRN Hospital Weinheim
Department of Cardiology, Angiology & Pneumology
Roentgenstrasse 1
69469 Weinheim
Germany

gkorosoglou@hotmail.com

Original communication

"Mixed Reality" in patient education prior to abdominal aortic aneurysm repair

A prospective, randomized, controlled pilot study

Johannes Hatzl, Niklas Hartmann, Dittmar Böckler, Daniel Henning, Andreas Peters, Katrin Meisenbacher, and Christian Uhl

Department of Vascular and Endovascular Surgery, University Hospital Heidelberg, Germany

Summary: *Background:* To investigate the usability of Mixed-Reality (MR) during patient education in patients scheduled for abdominal aortic aneurysm (AAA) repair. *Patients and methods:* Consecutive patients scheduled for elective AAA repair were block-randomized in either the Mixed-Reality group (MR group) or the conventional group (control group). Patients of both groups were educated about open and endovascular repair of their respective AAA. The MR group was educated using a head-mounted display (HMD) demonstrating a three-dimensional virtual reconstruction of the respective patient's vascular anatomy. The control group was educated using a conventional two-dimensional monitor to display the patient's vasculature. Outcomes were informational gain as well as patient satisfaction with the educational process. (DRKS-ID: DRKS00025174). *Results:* 50 patients were included with 25 patients in either group. Both groups demonstrated improvements in scores in the Informational Gain Questionnaire (IGQ) when comparing pre- and post-education scores. (MR group: 6.5 points (±1.8) versus 7.9 points (±1.5); Control group: 6.2 points (±1.8) versus 7.6 points (±1.6); $p<0.01$) There was no significant difference between the MR group and the control group either in informational gain (MR group: 1.4±1.8; Control group: 1.4±1.8; $p=0.5$) nor in patient satisfaction scores (MR group: mean 18.3 of maximum 21 points (±3.7); Control group: mean 17 of 21 points (±3.6); $p=0.1$) Multiple regression revealed no correlation between the use of MR and informational gain or patient satisfaction. Usability of the system was rated high, and patients' subjective assessment of MR was positive. *Conclusions:* The use of MR in patient education of AAA patients scheduled for elective repair is feasible. While patients reported positively on the use of MR in education, similar levels of informational gain and patient satisfaction can be achieved with MR and conventional methods.

Keywords: Mixed reality, augmented reality, virtual reality, abdominal aortic aneurysm, patient education, EVAR, open aortic repair

Introduction

"Mixed Reality" (MR) is an innovative technology that enables the projection of virtual objects into the physical environment and the users' field of view by wearing a head-mounted display (HMD) [1] (Figure 1). The terms MR and Augmented Reality (AR) are often used synonymously. While in MR and AR the physical environment remains visually perceptible and is augmented with digital information, in Virtual Reality (VR) the user is in a completely simulated environment [2]. MR and AR can be utilized to display three-dimensional virtual objects based on cross-sectional imaging like computed tomography angiography (CTA) (Figure 1). Furthermore, MR allows the user to interact with the virtual object either via a manual controller, gesture and/or voice control (electronic supplementary material [ESM] 1). Thereby, a three-dimensional, interactive model of a patient's individual anatomy can be created for a variety of applications. Among other areas, the use of MR in the field of patient education has recently been suggested [3, 4, 5, 6, 7, 8, 9]. A systematic review by Urlings et al. concluded with encouraging results regarding the potential of AR in patient education. It was also concluded however that evidence is limited and that existing studies often contain heterogenous applications and populations [10].

The use of MR in patient education prior to elective abdominal aortic aneurysm (AAA) repair might facilitate patient involvement in decision making in AAA management. A recent meta-analysis of available randomized, controlled trials has shown that EVAR is, despite its perioperative benefits, associated with an increased risk of AAA-related mortality, reintervention, and rupture in the long-term [11]. Additionally, comorbidity of patients complicates risk assessment. In this multifaceted context of management options, current guidelines recommend

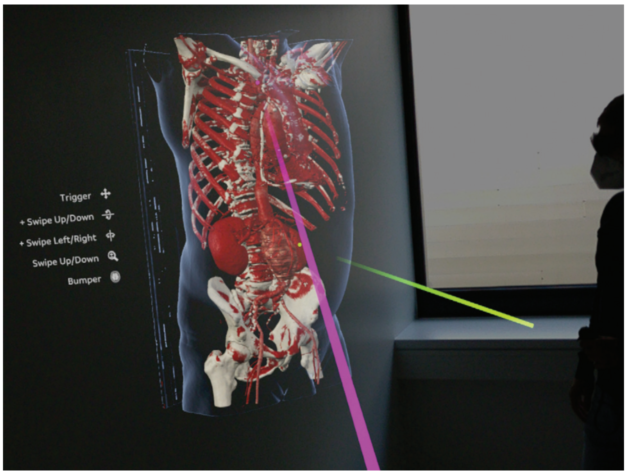


Figure 1. Observer's point of view. A virtual three-dimensional object is displayed in the physical environment. The object is based on a computer tomography angiography of a patient with an abdominal aortic aneurysm. The user can observe the object and interact with the model by wearing a head-mounted display (Magic Leap 1, Plantation, Florida, USA). A pointer can be used to highlight anatomic structures. Multiple observers can simultaneously observe and interact with the same model (Mixed Reality Viewer, Brainlab AG, Munich, Germany).

to also include the patient's personal preference in decision making [12, 13].

This should make high quality patient education a priority. It can empower the patient to make an informed decision, improve compliance, reduce anxiety and increase overall quality of healthcare [3, 14, 15, 16, 17]. And even though patient preference is one of the corner stones of decision making and highlighted in current guideline recommendations for AAA management, optimization of patient education is an underrepresented topic in the research landscape.

This prospective, randomized controlled pilot study investigates the feasibility of MR technology during patient education in patients scheduled for AAA repair. Furthermore, it explores whether MR can increase informational gain and patient satisfaction during patient education for open and endovascular repair options when compared to a control group.

Patients and methods

Study population

All consecutive patients that were scheduled for either open or endovascular repair for juxtarenal or infrarenal abdominal aortic aneurysms at the Department of Vascular and Endovascular Surgery at the University Hospital Heidelberg were considered for inclusion. Exclusion criteria were Age >80, inability to understand German language, emergency procedures, or presence of a legal guardianship. Patients were 1:1 block-randomized in either the MR group or the control group in a parallel design using a randomization list with a block length of 4. After screening and the patients' consent to participate, patients were allocated to a group according to the randomization list by a third person. Both groups were educated about open and endovascular AAA repair. Considering the pilot study design, sample size was set to 50 patients.

Patient education

In the MR group patient education was performed wearing an HMD (Magic Leap 1, Magic Leap, Florida, USA, Figure 2), by each the surgeon and the patient. Both were observing the same virtual, three-dimensional model of a patient-individual reconstruction of the vascular anatomy through the HMD (Mixed Reality Viewer, Brainlab AG, Munich, Germany, Figure 1). For the purposes of this study, only the surgeon was equipped with the manual controller and thereby enabled to interact with the model. The surgeon could zoom in and out of relevant structures as well as rotate the model. Additionally, using a pointer function, specific structures were highlighted for the patient. A video of operating the software is demonstrated in ESM 1.

In the control group, the pathology was visualized on a two-dimensional monitor using conventional viewing software (GE Centricity PACS RA1000 Workstation, Boston, Massachusetts, United States). The total duration of the process was timed. All education procedures were performed by the same surgeon to improve standardization of the procedure and increase comparability of results.

The surgeon educated all patients about the definition of an abdominal aortic aneurysm, the indication to repair, basic anatomical information including the location of the aneurysm relative to neighbouring organs and aortic branches, vascular access techniques including median laparotomy, femoral cut-down and percutaneous access, common complications following endovascular and open repair and follow-up protocols. The different methods of repair including endovascular, open, and as well as the distinct risks and benefits that are associated with each option were explained. Simultaneously, the patient-individual three-dimensional virtual object and important individual anatomical features such as for example the aneurysm neck, access vessels and other relevant structures were highlighted. Next, the steps of open and endovascular repair were explained. Patient education was performed in the hospital-setting prior to surgery.

MR workflow

The MR workstation consisted of a personal computer (PC) running the Elements Viewer software (Brainlab AG, Munich, Germany) as well as a Magic Leap 1 HMD. Based on a DICOM dataset of the preoperative computed tomography angiography an individual three-dimensional reconstruction of the patients' vascular anatomy was produced for every individual patient in the MR group. This process took a maximum of 10 minutes per patient.

After wireless imaging transport from the Elements Viewer to the Mixed Reality Viewer by visually scanning a QR-code as well as a positional marker, that ensures that

Figure 2. Mixed Reality workflow: Production of three-dimensional virtual objects is performed using the Mixed Reality Viewer (Brainlab AG, Munich, Germany). A Digital Imaging and Communications in Medicine (DICOM) dataset is uploaded to the software. The software automatically produces the virtual object that can be transferred to the head-mounted display by visually scanning a QR-code. Subsequently a positional marker is scanned to ensure the correct positioning for all simultaneous observers.

the object is on the same location in the room for both observers, the user can inspect and interact with the object. Up to four users can observe the same object simultaneously. The HMD furthermore allows the complete digital documentation of the educational process. The detailed workflow to create a three-dimensional virtual object is presented in Figure 3. No special training is required to operate the HMD as well as the Mixed Reality Viewer (Brainlab AG, Munich, Germany). Further technical specifications are presented in ESM 2.

Outcomes

Baseline demographics of all patients including age, gender, level of education and comorbidities are reported descriptively. All participants answered a questionnaire prior and after patient education about both the endovascular and open surgical repair options (Informational Gain Questionnaire (IGQ), 9 single-choice questions, maximum 9 points). Additionally, after patient education, the participants were asked to complete a questionnaire aimed at measuring the patients' satisfaction with the educational process (Patient Satisfaction Questionnaire (PSQ), 7 questions, each with a six-point Likert Scale, each question with −3 to +3 points, maximum 21 points). The MR group additionally completed a questionnaire specifically about the experience with using the HMD and its usability (MR Usability Questionnaire (MRUQ), 6 questions, each with a Six-Point Likert Scale). Unanswered items on the questionnaires were counted as false answers. It was ensured that during the education process, all information that is necessary to correctly answer the IGQ were explained to all patients in detail.

The primary outcome measures were informational gain and patient satisfaction with the patient education process. Informational gain was defined as the difference in score prior and following the patient education process in the IGQ. Patient satisfaction was measured as the total score achieved on the PSQ. Secondary outcomes were the duration of the patient education process as well as results of the MRUQ. English translation of the IGQ, PSQ and MRUQ are presented in Table I. Detailed questionnaires in English translation are presented in ESM 3, 4 and 5.

Statistical analysis

The study protocol was registered at the German Clinical Trials Register (DRKS-ID: DRKS00025174). The study was performed according to the Declaration of Helsinki and in accordance with the CONSORT statement [18]. Ethical approval was provided for the study by the local ethics committee (S-728/2020). Statistical analysis was performed using R [19]. Demographics are presented as mean±standard deviation as well as absolute and relative frequencies. Scores on the informational gain questionnaires as well as the patient satisfaction questionnaire are presented as mean±standard deviation and graphically displayed as Box-Whisker-Plots. The Wilcoxon test for two paired samples was performed to test for differences between the scores on the informational gain questionnaire pre- and post-education within the MR and control group,

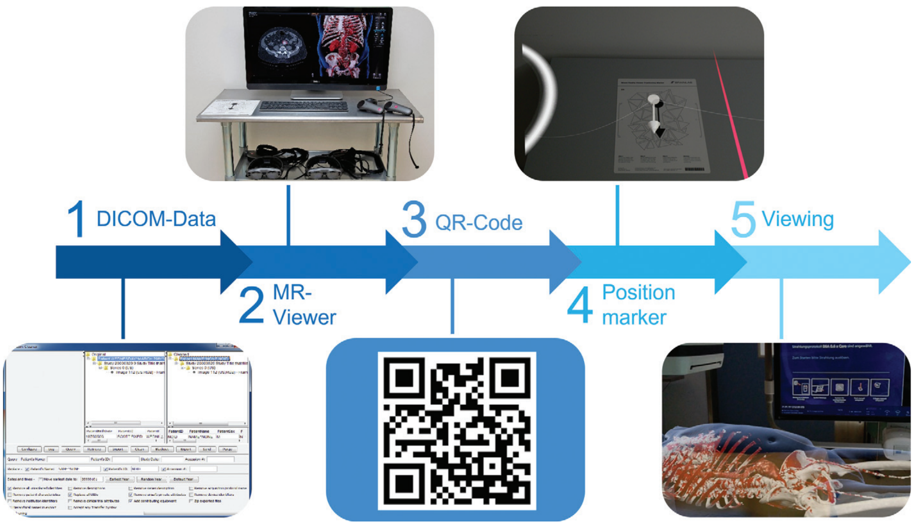


Figure 3. Magic Leap 1 (Plantation, Florida, USA).

Table I. Informational Gain Questionnaire (IGQ), Patient satisfaction questionnaire (PSQ) and Mixed Reality Usability Questionnaire (MRUQ)

Informational Gain Questionnaire (IGQ); Single-choice Questions

1. What is an aneurysm? *(Maximum 1 point)*
2. Why was I recommended to undergo surgery on my aneurysm? *(Maximum 1 point)*
3. What statement is correct about the postoperative period following open aneurysm repair? *(Maximum 1 point)*
4. Which of the following organs' location is closest to the operating field? *(Maximum 1 point)*
5. Which of the following surgical access techniques is commonly used for endovascular aneurysm repair? *(Maximum 1 point)*
6. Which of the following statements is generally true for endovascular aneurysm repair? *(Maximum 1 point)*
7. Which of the following complications can occur following endovascular aneurysm repair? *(Maximum 1 point)*
8. Which of the following statements is correct with regards to the follow-up protocol following endovascular aneurysm repair? *(Maximum 1 point)*
9. Which of the following statements comparing endovascular with open aneurysm repair is correct? *(Maximum 1 point)*

Patient Satisfaction Questionnaire (PSQ); Six-point Likert Scale

(Strongly agree, agree, somewhat agree, somewhat disagree, disagree, strongly disagree)

1. I felt time pressure. *(Maximum 3 points)*
2. The explanations were easy to follow. *(Maximum 3 points)*
3. Some of my questions remained unanswered. *(Maximum 3 points)*
4. I felt sufficiently informed. *(Maximum 3 points)*
5. I would have preferred a more descriptive form of patient education. *(Maximum 3 points)*
6. I do not feel sufficiently informed about potential complications. *(Maximum 3 points)*
7. Overall, I was pleased with the patient education process. *(Maximum 3 points)*

Mixed Reality Usability Questionnaire (MRUQ); Six-point Likert Scale

(*Strongly agree, agree, somewhat agree, somewhat disagree, disagree, strongly disagree*)

1. The handling of the HMD was impractical.
2. The use of the HMD made me feel uncomfortable (e.g., dizziness, headache, nausea).
3. The HMD helped me to better understand my disease.
4. The HMD helped me to better understand complications that can be associated with the procedure.
5. I feel like the use of the HMD during patient education is unnecessary.
6. In the future I would prefer if patient education in other specialties would also be performed using an HMD.

respectively. The Mann-Whitney-U-test for two unpaired samples was used to test for statistically significant differences of informational gain scores as well as patient satisfaction scores and the duration of patient educations between the MR and control groups. Multiple regression analysis was conducted to examine the correlation of the use of MR-assisted education, age, sex, level of education, baseline IGQ score, duration of education and ASA class with informational gain as well as patient satisfaction. For multiple regression, the categorical variable ASA (ASA 2, 3 and 4) was dummy coded with reference category 2.

Results

Study population

Between June 2021 and July 2022, fifty-five consecutive patients fulfilled the inclusion criteria. Five patients declined participation in the study. Fifty patients (91%) were included with a mean age of 68 years (±7.7) years in the MR group and 69 years (±8.1) in the control group. 12% of participants were female in either group. The mean AAA diameter was 5.6 cm (±1.0) and 5.7 cm (±0.6) in the MR and control group, respectively. Nine patients in the MR group (36%) and 6 patients in the control group (24%) had undergone higher education in their respective biographies. Comorbidities were similar between groups. Details with regards to the patient population including comorbidities are presented in Table II.

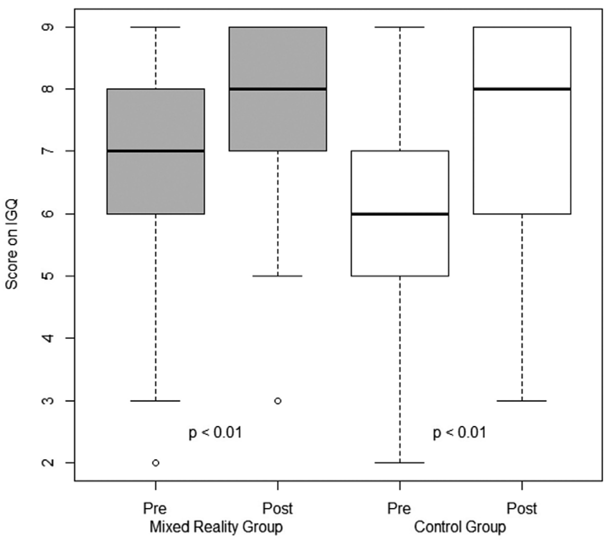
Informational gain

The MR group scored 6.5 (±1.8) points on the informational gain questionnaire prior to patient education and 7.9 (±1.5) points following patient education. The control group scored 6.2 (±1.8) and 7.6 (±1.6), respectively. In the MR group 22 of 25 patients improved their score (88%) while in the control group 23 of 25 patients (92%) could improve. Both groups demonstrated a significant increase in the achieved score on the IGQ ($p<0.01$). However, there was no significant difference in the mean increase between both groups with a mean difference in score of 1.4 points (±1.8) in each group ($p=0.5$). Scores on the IGQ prior and following patient education are presented in Figure 4. Informational gain is presented in Figure 5. Multiple regression analysis demonstrated that only the baseline IGQ score correlated with informational gain. Patients with a lower baseline score showed a greater informational gain. The use of MR, age, sex, level of education, duration of education as well as ASA class showed no correlation with informational gain in multiple regression analysis. Results of the multiple regression analysis are demonstrated in Table III.

Table II. Demographics of the MR group and the control group

	MR group (N=25)	Control group (N=25)
Mean age (±SD)	68 (±7.7)	69 (±8.1)
Female	3 (12%)	3 (12%)
BMI	27.4 (±3.9)	28.9 (±7.7)
Prop. of patients with higher education	9 (36%)	6 (24%)
Maximum AAA diameter	5.6 (±1.0)	5.7 (±0.6)
OAR	8 (32%)	6 (24%)
EVAR	17 (68%)	19 (76%)
ASA		
ASA 1	0	0
ASA 2	9 (36%)	6 (24%)
ASA 3	14 (56%)	19 (76%)
ASA 4	2 (8%)	0
ASA 5	0	0
Smoking		
Prior history of smoking	5 (20%)	8 (32%)
Current smoking	9 (36%)	13 (52%)
Hypertension	24 (96%)	22 (88%)
CAD	11 (44%)	12 (48%)
COPD	3 (12%)	6 (24%)
Diabetes mellitus		
Non-insulin-dependent	4 (16%)	4 (16%)
Insulin-dependent	0	2 (8%)
Neurological deficits		
Minor deficit	2 (8%)	1 (4%)
Major deficit	1 (4%)	0
In-hospital mortality	0 (0%)	0 (0%)

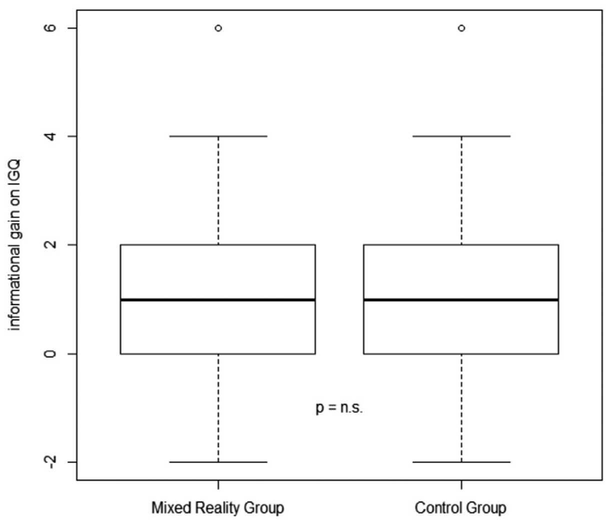
Notes. BMI: body-mass-index; OAR: open aortic repair; EVAR: endovascular aneurysm repair; SD: standard deviation; ASA: American Society of Anesthesiologists (ASA) classification; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease.



	Score pre-education	Score post-education	p value*
MR group (mean ± SD)	6.5 ± 1.8	7.9 ± 1.5	<0.01
Control group (mean ± SD)	6.2 ± 1.8	7.6 ± 1.6	<0.01

*Wilcoxon test for two paired samples.

Figure 4. Scores on the Informational Gain Questionnaire (IGQ) pre- and post- patient education in the MR- and control group.



	MR group	Control group	p-value*
Informational gain (mean ± SD)	1.4 ± 1.8	1.4 ± 1.8	0.5

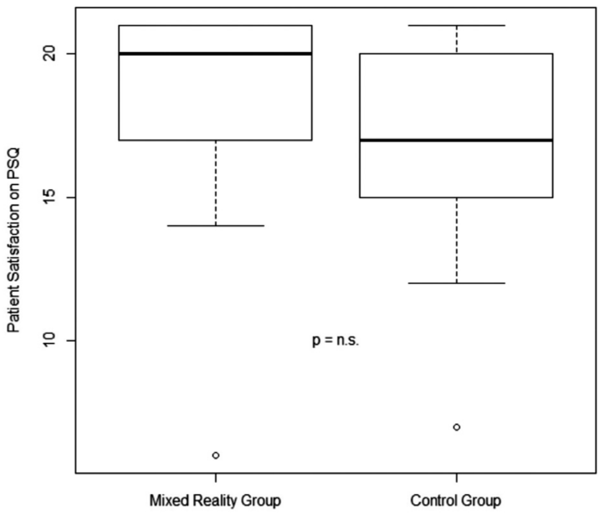
*Mann Whitney U test for two unpaired samples.

Figure 5. Informational gain in the MR- and control group according to the Informational Gain Questionnaire (IGQ).

Table III. Multiple regression analysis of informational gain

	Coefficient	SE	p value
Intercept	4.98	2.50	0.05
MR-group	0.01	0.44	0.98
Age	0.01	0.03	0.65
Female	0.77	0.67	0.26
Higher education	0.03	0.52	0.96
IGQ baseline score	−0.61	0.14	<0.05
Duration of patient education	−0.02	0.029	0.43
ASA class 3	−0.32	0.49	0.51
ASA class 4	0.15	1.30	0.91

Notes. ASA is categorical variable with 3 categories (2, 3 and 4) and was dummy-coded (reference category 2) for inclusion as predictor. SE: Standard Error; ASA: American Society of Anesthesiologists (ASA) classification.



	MR group	Control group	p-value*
Patient satisfaction score (mean ± SD)	18.3 ± 3.7	17 ± 3.6	0.1

*Mann Whitney U test for two unpaired samples.

Figure 6. Patient satisfaction in the MR- and control group according to the Patient Satisfaction Questionnaire (PSQ).

Patient satisfaction

The mean patient satisfaction score achieved by the MR group was 18.3 (±3.7) of a maximum of 21 points. The control group scored 17 (±3.6) points, respectively. There was no statistically significant difference in the scores achieved in the patient satisfaction questionnaire (p=0.1). Patient satisfactions scores are presented in Figure 6. Multiple regression analysis showed that patient satisfaction did not correlate with the use of MR, age, sex, duration, level of education as well as ASA class. Results of multiple regression are displayed in Table IV.

Duration of patient education

There were no significant differences in the duration of the patient education process with 22.5 (±9.3) min in the MR group and 21.6 (±5.7) min in the control group (p=0.69).

Table IV. Multiple regression analysis of patient satisfaction

	Coefficient	SE	p value
Intercept	14.1	6.4	0.03
MR-group	0.79	1.1	0.48
Age	−0.00	0.07	0.97
Female	−0.55	1.71	0.75
Higher education	0.56	1.3	0.68
IGQ baseline score	0.43	0.36	0.24
Duration of patient education	0.06	0.07	0.44
ASA class 3	−1.15	1.24	0.36
ASA class 4	2.63	3.30	0.43

Notes. ASA is categorical variable with 3 categories (2, 3 and 4) and was dummy-coded (reference category 2) for inclusion as predictor. SE: Standard Error; ASA: American Society of Anesthesiologists (ASA) classification.

Subjective assessment of MR usability

In the subjective assessment questionnaire 92% of patients reported that they agree or strongly agree that the use of the HMD has helped them to understand the disease. 96% strongly agreed or agreed that it helped to better understand complications associated with the procedure. 84% strongly agreed or agreed that in the future they would prefer other specialties to use MR in patient education as well. No patients reported that they felt that MR in patient education was unnecessary. 90% of patients strongly disagreed or disagreed that the handling of the HMD felt impractical. And no patients reported any discomfort with using the HMD. One patient did not answer questions 1–5. Detailed results from the subjective assessment of MR in patient education is presented in Table V.

Discussion

Previous studies have indicated promising results with the use of MR and AR technologies during patient education [4, 8]. Shared decision making in AAA repair needs to consider individual patient preference and risk assessment based on an underlying understanding of the disease. Surgeons are tasked with informing an often elderly and comorbid patient population about increasingly complex therapeutic options [20]. High quality patient education at the preoperative stage has the potential to increase compliance, reduce anxiety and thereby improve the overall quality of care [3, 14, 15, 16, 17, 21].

A recent scoping review about the state of shared decision making in the management of AAA concluded that even though AAA patients generally prefer shared decision making and despite it being a corner stone in current guideline recommendations, it is still underutilized in clinical practice. It was furthermore suggested that there is a need for decision support tools and training to facilitate shared decision making [22, 23, 24, 25, 26].

The present study demonstrated the feasibility of MR technology in AAA patients for educational purposes. Even

Table V. Subjective assessment of MR usability (MRUQ)

	Strongly agree	Agree	Rather agree	Rather disagree	Disagree	Strongly disagree
1. The handling of the HMD was impractical.	1/24 4%	0/24 0%	0/24 0%	1/24 4%	10/24 40%	12/24 50%
2. The use of the HMD made me feel uncomfortable (e.g., dizziness, headache, nausea).	0/24 0%	0/24 0%	0/24 0%	0/24 0%	5/24 21%	19/24 79%
3. The HMD helped me to better understand my disease.	17/24 71%	5/24 21%	1/24 4%	1/24 4%	0/24 0%	0/24 0%
4. The HMD helped me to better understand complications that can be associated with the procedure.	15/24 63%	8/24 33%	0/24 0%	1/24 4%	0/24 0%	0/24 0%
5. I feel like the use of the HMD during patient education is unnecessary.	0/24 0%	0/24 0%	0/24 0%	3/24 13%	8/24 33%	13/24 54%
6. In the future I would prefer it if patient education in other specialties would also be performed using an HMD.	17/25 68%	4/25 16%	3/25 13%	1/25 4%	0/25 0%	0/25 0%

though patients had a mean age of approximately 70 years, they were open to the technology, which is also reflected in a 91% participation rate in this study of a consecutive cohort of AAA patients scheduled for elective repair. This is in line with a previous study reporting on the use of VR in AAA patient education [27, 28]. Additionally, patients reported no adverse side effects like dizziness, headache, nausea, or discomfort and only one patient (4%) reported that the device was impractical. The usability of MR systems was generally rated high in the literature as well [9, 29, 30, 31].

Subjectively, patients evaluated MR very positively. Over 90% of patients agreed that MR has helped them to understand their disease and potential complications with the procedure. 96% said they would prefer patient education in other specialties to also be performed using MR. This is in line with results from previous studies exploring AR-, MR- or VR-technology [4, 9, 21, 28, 30, 32, 33].

However, statistical analysis including multiple regression revealed no correlation of informational gain or patient satisfaction with using MR. The only significant correlation that was identified demonstrates that patients with a lower baseline knowledge naturally benefit more from patient education, as expected. Interestingly, a high level of informational gain and patient satisfaction could be achieved in both groups. This might imply that rather than the use of MR, the stimulation of patients' involvement in the management decision was key, as was specified per protocol for both groups due to the study design. Similar observations were made previously in studies investigating the use of AR in education and teaching [9, 29, 30, 31, 34].

MR might be one way to keep patients engaged in their treatment. This is not necessarily exclusively true for MR and might as well apply for other kinds of decisional support tools. After all, high quality patient education needs to consider individual concerns and limitations as well. While patients and surgeons are tasked to reach a shared decision, it remains the surgeons' responsibility to adjust communication style and supporting tools to individual nneeds [35, 36].

Limitations

There are several limitations that need to be addressed. First it must be stated that these are single center results with a patient education intervention using one specific MR software application performed by a single surgeon and that results might not be generalizable. Future modifications of the application, such as labeling of anatomic structures and demonstration of educational images or video sequences in the MR environment might improve the performance of the application. Furthermore, this study only included patients with juxta- and infrarenal AAAs to increase comparability between groups. Thereby, it remains unknown if with increasing complexity of the procedures the potential benefit of MR visualization could be revealed. Second, while the questions to assess informational gain and patient satisfaction in this study were carefully selected, there were no validated instruments available to measure informational gain during patient education for AAA repair. In the future, patient preference, shared decision making, and health literacy will become increasingly important and standardized and validated tools to measure the quality of different methodological approaches are needed. Furthermore, at the time of patient education in the hospital setting, patients were already preinformed to varying degree from the out-patient setting. Different levels of prior knowledge could have introduced bias. Moreover, it was difficult to anticipate an adequate level of difficulty for the selected questions. Both limitations have led to relatively high baseline scores which left little room for improvement in either group. Third, the sample size of this pilot study was limited. While only one surgeon performed patient education interventions for both groups and informant bias was controlled, individual concerns and questions of patients leading to a deviation from the standard educational intervention could have resulted in information bias. Additionally, we did not include anxiety as well as mental status in our protocol, which could be confounding variables. For these reasons, the presented results must be interpreted as exploratory pilot study results. Despite the limitations, this is the largest series investigating MR education in a homogenous cohort of consecutive AAA patients with a respective control group and in a randomized setting.

Conclusions

The use of MR in patient education of AAA patients scheduled for elective repair is feasible. While patients reported very positively on MR-assisted education, similar levels of informational gain and patient satisfaction can be achieved with conventional methods.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a001062

ESM 1. Use of the mixed reality viewer application (Video)

ESM 2. Technical specifications of the Magic Leap One Head-mounted Display (Table)

ESM 3. Informational Gain Questionnaire (IGQ)

ESM 4. Mixed Reality Usability Questionnaire (MRUQ)

ESM 5. Patient Satisfaction Questionnaire (PSQ)

References

1. Hu HZ, Feng XB, Shao ZW, Xie M, Xu S, Wu XH, et al. Application and prospect of mixed reality technology in medical field. Curr Med Sci. 2019;39(1):1–6. https://doi.org/10.1007/s11596-019-1992-8
2. Milgram P, Takemura H, Utsumi A, Kishino F. Augmented reality: a class of displays on the reality-virtuality continuum. SPIE. 1995;2351. https://doi.org/10.1117/12.197321
3. Hill J, Bird H, Johnson S. Effect of patient education on adherence to drug treatment for rheumatoid arthritis: a randomised controlled trial. Ann Rheum Dis. 2001;60(9):869–75.
4. House PM, Pelzl S, Furrer S, Lanz M, Simova O, Voges B, et al. Use of the mixed reality tool "VSI Patient Education" for more comprehensible and imaginable patient educations before epilepsy surgery and stereotactic implantation of DBS or stereo-EEG electrodes. Epilepsy Res. 2020;159:106247. https://doi.org/10.1016/j.eplepsyres.2019.106247
5. Sezer S, Piai V, Kessels RPC, Ter Laan M. Information recall in pre-operative consultation for Glioma surgery using actual size three-dimensional models. J Clin Med. 2020;9(11):3660. https://doi.org/10.3390/jcm9113660
6. Bork F. Interactive augmented reality systems: Aid for personalized patient education and rehabilitation. Unfallchirurg. 2018;121(4):286–92. https://doi.org/10.1007/s00113-018-0458-y
7. Lo SJ, Chapman P, Young D, Drake D, Devlin M, Russell C. The Cleft Lip Education with Augmented Reality (CLEAR) VR Phase 2 Trial: a pilot randomized crossover trial of a novel patient information leaflet. Cleft Palate Craniofac J. 2022;60(2). https://doi.org/10.1177/10556656211059709
8. Lee JJ, Klepcha M, Wong M, Dang PN, Sadrameli SS, Britz GW. The first pilot study of an interactive, 360° augmented reality visualization platform for neurosurgical patient education: a case series. Oper Neurosurg. 2022;23(1):53–9. https://doi.org/10.1227/ons.0000000000000186
9. Wake N, Rosenkrantz AB, Huang R, Park KU, Wysock JS, Taneja SS, et al. Patient-specific 3D printed and augmented reality kidney and prostate cancer models: impact on patient education. 3D Print Med. 2019;5(1):4. https://doi.org/10.1186/s41205-019-0041-3
10. Urlings J, Sezer S, Ter Laan M, Bartels R, Maal T, Boogaarts J, et al. The role and effectiveness of augmented reality in patient education: a systematic review of the literature. Patient Educ Couns. 2022;105(7):1917–27. https://doi.org/10.1016/j.pec.2022.03.005
11. Antoniou GA, Antoniou SA, Torella F. Editor's choice – Endovascular vs. open repair for abdominal aortic aneurysm: systematic review and meta-analysis of updated peri-operative and long term data of randomised controlled trials. Eur J Vasc Endovasc Surg. 2020;59(3):385–97. https://doi.org/10.1016/j.ejvs.2019.11.030
12. Debus ES. S3-leitlinie zum screening, diagnostik therapie und nachsorge des bauchaortenaneurysmas. Gefässchirurgie. 2018;23(6):402–3. https://doi.org/10.1007/s00772-018-0452-2
13. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's choice – European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. Eur J Vasc Endovasc Surg. 2019;57(1):8–93. https://doi.org/10.1016/j.ejvs.2018.09.020
14. Gold DT, McClung B. Approaches to patient education: emphasizing the long-term value of compliance and persistence. Am J Med. 2006;119(4 Suppl 1):S32–7. https://doi.org/10.1016/j.amjmed.2005.12.021
15. Guo P, East L, Arthur A. A preoperative education intervention to reduce anxiety and improve recovery among Chinese cardiac patients: a randomized controlled trial. Int J Nurs Stud. 2012;49(2):129–37. https://doi.org/10.1016/j.ijnurstu.2011.08.008
16. Marcus C. Strategies for improving the quality of verbal patient and family education: a review of the literature and creation of the EDUCATE model. Health Psychol Behav Med. 2014;2(1):482–95. https://doi.org/10.1080/21642850.2014.900450
17. Yeh MY, Wu SC, Tung TH. The relation between patient education, patient empowerment and patient satisfaction: a cross-sectional-comparison study. Appl Nurs Res. 2018;39:11–7. https://doi.org/10.1016/j.apnr.2017.10.008
18. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726–32. https://doi.org/10.7326/0003-4819-152-11-201006010-00232
19. R Studio Team. RStudio: integrated development environment for R [computer software]. Boston, MA: RStudio, PBC; 2021.
20. O'Donnell TFX, Patel VI, Deery SE, Li C, Swerdlow NJ, Liang P, et al. The state of complex endovascular abdominal aortic aneurysm repairs in the vascular quality initiative. J Vasc Surg. 2019;70(2):369–80. https://doi.org/10.1016/j.jvs.2018.11.021
21. Yang JH, Ryu JJ, Nam E, Lee HS, Lee JK. Effects of preoperative virtual reality magnetic resonance imaging on preoperative anxiety in patients undergoing arthroscopic knee surgery: a randomized controlled study. Arthroscopy. 2019;35(8):2394–9. https://doi.org/10.1016/j.arthro.2019.02.037
22. Machin M, Van Herzeele I, Ubbink D, Powell JT. Shared decision making in and management of intact abdominal aortic aneurysm: a scoping review of the literature. Eur J Vasc Endovasc Surg. 2023. https://doi.org/10.1016/j.ejvs.2023.01.036
23. Stubenrouch FE, Peters LJ, de Mik SML, Klemm PL, Peppelenbosch AG, Schreurs S, et al. Improving shared decision making in vascular surgery: a stepped wedge cluster randomised trial. Eur J Vasc Endovasc Surg. 2022;64(1):73–81. https://doi.org/10.1016/j.ejvs.2022.04.016
24. Eid MA, Barry MJ, Tang GL, Henke PK, Johanning JM, Tzeng E, et al. Effect of a decision aid on agreement between patient

preferences and repair type for abdominal aortic aneurysm: a randomized clinical trial. JAMA Surg. 2022;157(9):e222935. https://doi.org/10.1001/jamasurg.2022.2935
25. Knops AM, Goossens A, Ubbink DT, Balm R, Koelemay MJ, Vahl AC, et al. A decision aid regarding treatment options for patients with an asymptomatic abdominal aortic aneurysm: a randomised clinical trial. Eur J Vasc Endovasc Surg. 2014; 48(3):276–83. https://doi.org/10.1016/j.ejvs.2014.04.016
26. de Mik SML, Stubenrouch FE, Balm R, Ubbink DT. Development of three different decision support tools to support shared decision-making in vascular surgery. Patient Educ Couns. 2021;104(2):282–9. https://doi.org/10.1016/j.pec.2020.11.036
27. Pandrangi VC, Gaston B, Appelbaum NP, Albuquerque FC, Levy MM, Larson RA. The application of virtual reality in patient education. Ann Vasc Surg. 2019;59:184–9. https://doi.org/10.1016/j.avsg.2019.01.015
28. van der Linde-van den Bor M, Slond F, Liesdek OCD, Suyker WJ, Weldam SWM. The use of virtual reality in patient education related to medical somatic treatment: a scoping review. Patient Educ Couns. 2022;105(7):1828–41. https://doi.org/10.1016/j.pec.2021.12.015
29. Brown HM, Collins CE, Bucher T, Rollo ME. Evaluation of the effectiveness and usability of an educational portion size tool, ServARpreg, for pregnant women. J Hum Nutr Diet. 2019; 32(6):719–27. https://doi.org/10.1111/jhn.12660
30. Bray L, Sharpe A, Gichuru P, Fortune PM, Blake L, Appleton V. The acceptability and impact of the Xploro digital therapeutic platform to inform and prepare children for planned procedures in a hospital: before and after evaluation study. J Med Internet Res. 2020;22(8):e17367. https://doi.org/10.2196/17367
31. Tait AR, Connally L, Doshi A, Johnson A, Skrzpek A, Grimes M, et al. Development and evaluation of an augmented reality education program for pediatric research. J Clin Transl Res. 2020;5(3):96–101.
32. Azman A, Poyade M, Overell J. Towards a more user-friendly medication information delivery to people living with multiple sclerosis: a case study with Alemtuzumab. Adv Exp Med Biol. 2019;1120:67–82. https://doi.org/10.1007/978-3-030-06070-1_6
33. Bekelis K, Calnan D, Simmons N, MacKenzie TA, Kakoulides G. Effect of an immersive preoperative virtual reality experience on patient reported outcomes: a randomized controlled trial. Ann Surg. 2017;265(6):1068–73. https://doi.org/10.1097/sla.0000000000002094
34. Bölek KA, De Jong G, Henssen D. The effectiveness of the use of augmented reality in anatomy education: a systematic review and meta-analysis. Sci Rep. 2021;11(1):15292. https://doi.org/10.1038/s41598-021-94721-4
35. Wang LYT, Lua JYH, Chan CXC, Ong RLL, Wee CF, Woo BFY. Health information needs and dissemination methods for individuals living with ischemic heart disease: a systematic review. Patient Educ Couns. 2023;108:107594. https://doi.org/10.1016/j.pec.2022.107594
36. World Health Organization, Therapeutic patient education: continuing education programmes for health care providers in the field of prevention of chronic diseases: report of a WHO working group. Copenhagen: World Health Organization; 1998.

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ORCID
Johannes Hatzl
https://orcid.org/0000-0002-3152-7791
Niklas Hartmann
https://orcid.org/0000-0002-8442-0752
Andreas Peters
https://orcid.org/0000-0002-1347-7575

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Correspondence address
Dr. med. Johannes Hatzl
Department of Vascular and Endovascular Surgery
University Hospital Heidelberg
Im Neuenheimer Feld 420
69120 Heideberg
Germany

johannes.hatzl@web.de

Original communication

Outcomes of endovascular repair of infrarenal penetrating aortic ulcers

Insights from the abdominal aortic aneurysm registry of the German Institute for Vascular Research

Johannes Hatzl[1], Christian-Alexander Behrendt[2], Thomas Schmitz-Rixen[2], Reinhart Thomas Grundmann[2], Markus Steinbauer[4,5], Dittmar Böckler[1], and Christian Uhl[1] for the DIGG Investigators

[1] Department of Vascular and Endovascular Surgery, University Hospital Heidelberg, Germany
[2] German Institute for Vascular Research (DIGG gGmbH), Berlin, Germany
[3] Asklepios Clinic Wandsbek, Asklepios Medical School Hamburg, Germany
[4] German Society of Vascular Surgery and Vascular Medicine (DGG e.V.), Berlin, Germany
[5] Department of Vascular Surgery, Barmherzige Brüder Hospital, Regensburg, Germany

Summary: *Background:* To report technical success as well as perioperative outcomes of patients who underwent endovascular aortic repair (EVAR) of penetrating abdominal aortic ulcers ≤35 mm in diameter (PAU). *Patients and methods:* The abdominal aortic aneurysm (AAA) quality registry of the German institute for vascular research (DIGG) was used to identify patients with standard EVAR for infrarenal PAU ≤35 mm between 1/1/2019 and 12/31/2021. Infectious, traumatic, inflammatory PAUs, PAUs associated with connective tissue disease, PAUs following aortic dissection as well as true aneurysms were excluded. Demographics, cardiovascular comorbidity, technical success as well as perioperative morbidity and mortality were determined. *Results:* Amongst 11 537 patients who underwent EVAR during the study period, 405 with PAU ≤35 mm were eligible from 95 participating hospitals across Germany (22% women, 20.5% octogenarians). The median aortic diameter was 30 mm (Interquartile range 27–33). Cardiovascular comorbidities were frequent with coronary artery disease (34.8%), chronic heart failure (30.9%), history of myocardial infarction (19.8%), hypertension (76.8%), diabetes (21.7%), smoking (20.8%), history of stroke (9.4%), symptomatic lower extremity peripheral arterial disease (20%), chronic kidney disease (10.4%) and chronic obstructive pulmonary disease (9.6%). Most patients were asymptomatic (89.9%). Among the symptomatic patients, 13 presented with distal embolization (3.2%) and 3 with contained ruptures (0.7%). Technical success of endovascular repair was 98.3%. Both, percutaneous (37.1%) or femoral cut-down access approaches (58.5%) were registered. Endoleaks of any type were present with type 1 (0.5%), type 2 (6.4%) and type 3 (0.3%) endoleaks. Overall mortality was 0.5%. Perioperative complications occurred in 12 patients (3.0%). *Conclusions:* According to this registry data, endovascular repair of PAU is technically feasible with acceptable perioperative outcomes, but further studies investigating mid- and long-term data are needed before invasive treatment of PAU disease in an elderly and comorbid patient population should be recommended.

Keywords: Aorta, PAU, aneurysm, atherosclerosis, EVAR, endovascular

Introduction

Penetrating aortic ulcer (PAU) is defined as an ulceration that penetrates the internal elastic lamina and allows hematoma formation within the media of the aortic wall [1]. With wide-spread use of computed tomography angiography asymptomatic PAU has become a relevant incidental finding from opportunistic screening. The European Society for Vascular Surgery (ESVS) 2019 Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms recommended serial imaging in uncomplicated cases and invasive repair in patients with complicated PAU. Factors which usually indicate complicated lesions comprise extra-aortic hematoma, embolization symptoms, recurrent pain, a PAU that initially measures >20 mm in width or >10 mm in depth or progression of total aortic diameter [2]. However, the decision to repair asymptomatic patients may be challenging. A recently published study by DeCarlo et al. examining small PAUs with a mean aortic diameter of 31.4 mm (95% confidence interval, CI, 30.1–32.7)

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concluded that asymptomatic PAU was associated with a benign natural course with a cumulative incidence of PAU-related complications of 6.5% at 10 years after diagnosis [3]. This raises the question of outcomes of endovascular repair in these patients to facilitate risk assessment. Evidence on both, technical and clinical outcomes of endovascular treatment of patients with abdominal PAU remains limited to small retrospective observational series with mainly short-term follow-up [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20].

This study aimed to determine perioperative outcomes of patients who underwent endovascular repair of small PAU (≤35 mm). We used German-wide data of the abdominal aortic aneurysm (AAA) quality assurance registry of the German Institute for Vascular Research (DIGG).

Patients and methods

The AAA quality assurance registry of the German Institute for Vascular Research (DIGG) consecutively collects data from more than 120 centers (2022) and was used for this study. All patients who underwent endovascular or open repair for AAA, PAU and abdominal aortic dissection are eligible for the registry. Data is manually entered into a web-based case-report-form. Participation is voluntary for all centers.

In this registry-based retrospective observational study, all patients treated with endovascular aortic repair (EVAR) for infrarenal PAU with a maximum diameter ≤35 mm between 1/1/2019 and 12/31/2021 were included. Infectious, traumatic, inflammatory PAUs, PAUs associated with connective tissue disease and PAUs secondary to aortic dissection as well as true aneurysms were excluded. Patients with juxtarenal, pararenal or suprarenal PAUs as well as patients who underwent fenestrated, branched or chimney EVAR were also excluded.

Abdominal PAU is defined as a focal, localized outpouching of contrast material in the presence of atherosclerosis with a variable extent of intramural hematoma [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20].

Ethical approval was provided by the Institutional Review Board of the University Hospital Heidelberg (S-806/2020). The study was conducted according to STROBE guidelines [21].

Outcomes

Baseline demographics, cardiovascular comorbidity, maximum aortic diameter (in mm, outer-to-outer diameter), basic procedural data with technical success, and perioperative clinical outcomes are reported. Technical success was defined as successful delivery and deployment of the device without unintentional coverage of renal or internal iliac arteries and without type 1 or type 3 endoleak at completion [22].

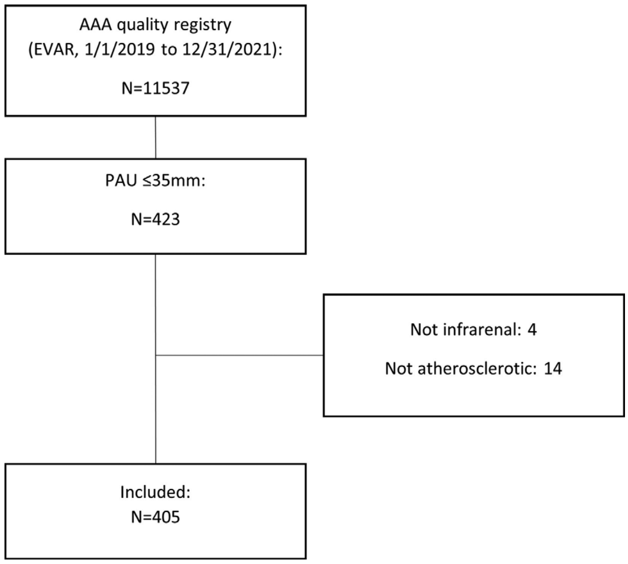

Figure 1. Patient population.

Statistical analysis

Results are presented descriptively with median and interquartile range (IQR) as well as mean and standard deviation (SD). Proportions were reported with %. Missing data was handled by case wise exclusion. Statistical analysis was performed using the statistic software R [23].

Results

Patient population

Between 1/1/2019 and 12/31/2021, 405 patients (3.5%) treated at 95 participating hospitals (median 4.3 patients per hospital) fulfilled the inclusion criteria. Patient population is displayed in Figure 1.

Comorbidity and cardiovascular risk factors

Eighty-nine (22.0%) patients were female. Eighty-three (20.5%) patients were ≥ 80 years of age. The median maximum aortic diameter was 30 mm (IQR: 27–33, mean: 29.2, SD: 5.3), minimum: 10, maximum: 35). Median Body-Mass-Index was 25.6 (IQR 23.4–28.7, mean: 26.2, SD: 4.3).

A total of 141 patients (34.8%) had coronary artery disease. 125 (30.9%) had chronic heart failure. Three hundred and eleven (76.8%) had hypertension, 88 (21.7%) had diabetes, 82 (20.2%) were smokers and 80 (19.8%) patients had a history of myocardial infarction. Thirty-eight (9.4%) patients had a history of stroke and 81 (20.0%) patients had a history of symptomatic lower extremity peripheral arterial disease. Chronic kidney disease was present in 42 (10.4%) patients with 7 (1.7%) patients having an estimated glomerular filtration rate <30 ml/min/1.73 m^2.

Table I. Demographics

	Absolute frequency (N)	Relative frequency (%)
Demographics (N=404)		
Age≥80 years (octogenarians)	83	20.5%
Female	89	22.0%
ASA class (N=401)		
ASA 1	4	0.1%
ASA 2	104	25.9%
ASA 3	269	67.1%
ASA 4	19	4.7%
ASA 5	1	0.02%

Notes. ASA class: American Society of Anesthesiologists classification.

Thirty-nine (9.6%) patients had chronic obstructive pulmonary disease.

A total of 269 (66.4%) patients were classified as having severe systemic disease (American Society for Anesthesiology, ASA class 3) and 19 (4.7%) had a constant threat to life (ASA class 4). Comorbidities are presented in Tables I and II.

Clinical presentation

Most patients (364, 89.9%) were treated for asymptomatic PAU. The remaining 41 (11.1%) patients were treated for symptomatic PAU. Of these, the symptoms comprised distal embolization in 13 (3.2%) cases as well as 3 (0.7%) contained ruptures. The remaining 25 patients' symptoms were neither embolization nor rupture, but not specified in detail.

Baseline demographics andcomorbidities, are summarized in Tables I and II.

Technical success, endoleaks, postoperative hospital length of stay

One hundred and forty-nine (36.4%) patients were treated via a bilateral percutaneous and 253 (58.5%) via a bilateral cut-down vascular access or unilateral cut-down and contralateral percutaneous access (4.5%). Forty-five (11.1%) patients required either femoral reconstruction or iliac angioplasty with or without stent implantation. Endoleaks of any type were present with type 1 (0.6%), type 2 (6.5%) and type 3 (0.2%) endoleaks. The status with regards to unintentional coverage of renal and/or internal iliac arteries was reported for only 361 patients. Among these, there were two (0.5%) unintentional stentgraft-associated renal artery occlusions. Additionally, there was one (0.2%) open surgical conversion, resulting in a technical success rate according to the above-mentioned definition of 355/361 (98.3%). Postoperative complications occurred in 12 (3.0%) patients. The median postoperative length of hospital stay was 5 days (IQR: 4–6) and 14 (3.5%) patients required treatment on the intensive care unit (ICU) >1 day. Seven (1.7%) patients required blood transfusion.

Table II. Comorbidities

Comorbidities (N=405)	Absolute frequency (N)	Relative frequency (%)
Coronary artery disease	141	34.8%
Chronic heart failure	125	30.9%
History of myocardial infarction	80	19.8%
Symptomatic lower extremity peripheral arterial disease	81	20.0%
History of stroke	38	9.4%
Chronic kidney disease	42	10.4%
eGFR <30 ml/min/1.73 m^2 (N=404)	7	1.7%
Chronic obstructive pulmonary disease	39	9.6%
Malignancy	29	7.2%
Diabetes	88	21.7%
Hypertension	311	76.8%
Dyslipoproteinemia	90	22.2%
Smoking	82	20.2%

Notes. eGFR: estimated glomerular filtration rate.

Table III. Procedural details and endoleaks

	Absolute frequency (N)	Relative frequency (%)
Technical success (N=361)	355	98.3%
Open conversion (N=405)	1	0.3%
Unintentional coverage of aortic branches (N=361)		
One or both renal arteries	2	0.6%
One or both internal iliac arteries	0	0%
Intentional coverage of aortic branches (N=361)		
One renal artery	1	0.3%
One or both internal iliac arteries	5	1.4%
Endoleaks (N=405)		
Type 1a endoleak	2	0.5%
Type 1b endoleak	0	0%
Type 2 endoleak	26	6.4%
Type 3 endoleak	1	0.3%
Vascular access (N=405)		
Percutaneous	149	37.1%
Cut-down	235	58.5%
Both	18	4.5%
Adjunctive procedures (N=405)		
Iliac balloon angioplasty/stent	31	7.7%
Femoral reconstruction	14	3.5%
Iliac-branched device	18	4.4%

Two patients (0.5%) with an asymptomatic PAU died during the hospital stay. The detailed sequelae that led to death could not be extracted. Procedural details, endoleaks, and complications are presented in Tables III and IV.

Table IV. Mortality and systemic complications

	Asymptomatic (N=364)		Symptomatic (N=41)		Total (N=405)	
	N	%	N	%	N	%
Overall mortality	2	0.5%	0	0%	2	0.5%
Systemic complications (N=405)						
Postoperative urinary tract infection	4	1.1%	0	0.0%	4	1.0%
Postoperative pneumonia	3	0.8%	0	0.0%	3	0.7%
Postoperative myocardial infarction	2*	0.5%	1	2.4%	3*	0.7%
Postoperative heart failure	0	0.0%	0	0.0%	0	0.0%
Postoperative stroke	1	0.3%	0	0.0%	1	0.2%
Postoperative kidney failure	1*	0.3%	0	0.0%	2*	0.5%
Total	11	3.0%	1	2.4%	12	3.0%

Notes. *One postoperative myocardial infarction and one kidney failure occurred in the same patient.

Discussion

The present study determined acceptable perioperative morbidity and mortality of endovascular repair of small PAU over a 3-year period from a German-wide national quality improvement registry. Evidence on the management of patients with abdominal PAU is limited to case series and small observational studies with generally short periods of follow-up [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24]. Data on the natural history of this entity in the abdominal aorta is also limited, thereby hampering decision making in clinical practice. A recent single-center study has demonstrated a rather benign natural history in 97 patients with small abdominal PAUs with a mean diameter of 31.4 mm and a low PAU-related complication rate at 10 years after diagnosis [3].

In the present registry cohort, only 10% of patients were symptomatic and only 3 (0.7%) patients presented with contained ruptures at the time of treatment, which is lower than in previous studies reporting 25–100% for symptoms and 0–32% for ruptures [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19].

This might indicate a more liberal indication to repair in the German healthcare system for small PAU over the study period when compared to previous studies and is in line with the suggestion of a rather benign natural history of small PAU disease [3]. When compared to true abdominal aortic aneurysm disease undergoing repair (AAA), the previously published data from the German institute for vascular research from 2019 reported a proportion of 9.7% ruptured AAA compared to a rupture rate of 0.7% for small PAU in the present study [25].

High technical success rates with endovascular repair for abdominal PAU have been continuously reported in the literature [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24]. Accordingly, the rates of type 1 and 3 endoleaks were low, as was the incidence of type 2 endoleak which is indicative of the focal nature of abdominal PAU disease with involvement of potentially less infrarenal aortic branches when compared to abdominal aortic aneurysm disease.

While in most patients endovascular repair was technically successful, as expected, the minimally invasive treatment of PAU was still associated with considerable mortality and morbidity. Interestingly, about two thirds of patients were treated via a femoral cut-down access which is associated with prolonged hospitalization. Additionally, about 10% of patients required adjunctive procedures such as femoral artery reconstruction or iliac angioplasty with or without stent implantation, which demonstrates the atherosclerotic burden of these patients. Overall, morbidity and mortality were within an acceptable range for endovascular repair and similar like in previous reports [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. However, all potential technical and clinical complications must be weighed in against the risk that is associated with the natural history of the disease [3]. Furthermore, data on mid- and long-term outcomes with the potential of late complications such as limb occlusion are lacking. Considering the benign natural history of small abdominal PAUs and the comorbidity of the cohort in this study as well as the unknown overall long-term prognosis of these elderly patients, invasive treatment early after diagnosis should not be recommended. Instead, until further evidence is available, imaging surveillance 3 months after initial diagnosis and reevaluation of repair appears to be a reasonable management strategy as was previously suggested [3]. Additionally, further observational studies with long-term follow-up are required to gain an understanding of the natural course of this pathology and to enable more accurate assessment of its associated risks.

Limitations

There are several limitations of the present study that need to be considered. First, this is a retrospective analysis of registry data which naturally limits data quality, also due to missing data. While data of 95 participating hospitals could be included, the degree of detail is limited. Important data like aortic morphology especially width and depth of the PAU, devices used, including configuration, as well as more detailed data on comorbidity, clinical presentation, and complications are lacking. Furthermore, there were no unified definitions used for comorbidities. Eight (2.0%) patients were reported to have a maximum aortic diameter <15 mm. This might be erroneous data or patients that were treated for penetrating ulcer of the common iliac artery. It illustrates one of the major limitations of the study, that there was no original imaging available for review. This can also be an indicator for the application of different diagnostic criteria applied by the different vascular surgeons involved in the treatment of PAU patients which could have introduced bias and implicates a need for a unified and precise nomenclature and core-laboratory assessment of PAU studies. Second, it needs to be acknowledged that not all patients treated during that period have been entered into the registry, which results in the potential of selection bias. The detailed rationale for repair in the participating hospitals remains unknown after all. Therefore, results might not be generalizable. Furthermore, there was no data on follow up as well as no sufficient data on reinterventions available for analysis. Moreover, this study only included standard EVAR. More recently, balloon-expandable stent grafts have been used in infrarenal PAU disease with promising initial results. The optimal endovascular management strategy has yet to be determined.

Despite these limitations, this is to our knowledge the largest series reporting on perioperative outcomes of endovascular repair of small PAU. This study provides an estimate of the associated morbidity and mortality of endovascular repair based on nation-wide data. It was furthermore shown that despite its rarity asymptomatic PAU disease is of relevance for clinical practice and requires further research with mid-term and long-term follow-up data to allow more definite clinical practice guidelines.

Conclusions

Based on this registry data, endovascular repair was associated with high technical success and acceptable perioperative morbidity and mortality in patients with small PAU. However, a higher level of evidence, a better understanding of the natural history of abdominal PAU disease and associated rupture risks are needed before invasive treatment in asymptomatic patients should be recommended.

References

1. Stanson AW, Kazmier FJ, Hollier LH, Edwards WD, Pairolero PC, Sheedy PF, et al. Penetrating atherosclerotic ulcers of the thoracic aorta: natural history and clinicopathologic correlations. Ann Vasc Surg. 1986;1(1):15–23.
2. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019;57(1):8–93.
3. DeCarlo C, Latz CA, Boitano LT, Kim Y, Tanious A, Schwartz SI, et al. Prognostication of asymptomatic penetrating aortic ulcers: a modern approach. Circulation. 2021;144(14):1091–101.
4. Batt M, Haudebourg P, Planchard PF, Ferrari E, Hassen-Khodja R, Bouillanne PJ. Penetrating atherosclerotic ulcers of the infrarenal aorta: life-threatening lesions. Eur J Vasc Endovasc Surg. 2005;29(1):35–42.
5. Georgiadis GS, Trellopoulos G, Antoniou GA, Georgakarakos EI, Nikolopoulos ES, Pelekas D, et al. Endovascular therapy for penetrating ulcers of the infrarenal aorta. ANZ J Surg. 2013; 83(10):758–63.
6. Hyhlik-Dürr A, Geisbüsch P, Kotelis D, Böckler D. Endovascular repair of infrarenal penetrating aortic ulcers: a single-center experience in 20 patients. J Endovasc Ther. 2010;17(4):510–4.
7. Jones DW, Meltzer AJ, Graham AR, Connolly PH, Bush HL, Schneider DB. Endovascular repair of infrarenal focal aortic pathology with limited aortic coverage. Ann Vasc Surg. 2014;28(5):1316.e15–22.
8. Kazan V, Jamil T, Beyrouti R, Nazzal M. Penetrating abdominal aortic ulcers: case reports and review of the literature. Vascular. 2011;19(6):346–50.
9. Kruszyna Ł, Dzieciuchowicz Ł, Strauss E, Oszkinis G. Midterm results of the treatment of penetrating abdominal aortic or iliac artery ulcer with the BeGraft balloon-expandable covered stent – a single-center experience. Ann Vasc Surg. 2020;69:382–90.
10. Palombo D, Lucertini G, Robaldo A, Pane B, Spinella G. Treatment of penetrating aortic ulcer by endoprosthesis: a single center experience. Int Angiol. 2012;31(1):54–61.
11. Piffaretti G, Tozzi M, Lomazzi C, Rivolta N, Caronno R, Castelli P. Endovascular repair of abdominal infrarenal penetrating aortic ulcers: a prospective observational study. Int J Surg. 2007;5(3):172–5.
12. Stana J, Fernandez Prendes C, Kruszyna L, Passaloglou IT, Ruffino MA, Reyes Valdivia A, et al. Multicenter experience with large diameter balloon-expandable stent-grafts for the treatment of infrarenal penetrating aortic ulcers. J Endovasc Ther. 2021;28(6):871–7.
13. Tsuji Y, Tanaka Y, Kitagawa A, Hino Y, Taniguchi T, Sugimoto K, et al. Endovascular stent-graft repair for penetrating atherosclerotic ulcer in the infrarenal abdominal aorta. J Vasc Surg. 2003;38(2):383–8.
14. Wagenhäuser MU, Floros N, Nikitina E, Mulorz J, Balzer KM, Goulas S, et al. Use of the AFX stent graft in patients with extremely narrow aortic bifurcation: a multicenter retrospective study. Int J Vasc Med. 2021;2021:7439173.
15. Yao C, Ning J, Li Z, Wang M, Wu R, Wang S, et al. Parallel covered stents technique in the treatment of abdominal aortic diseases. J Vasc Interv Radiol. 2020;31(5):771–7.
16. Yoshida RA, Costa RF, Cunha DO, Palhares RM, Jaldin RG, Sobreira ML, et al. Unibody design for aortic disease with a narrow aortic bifurcation: tips and tricks for success. J Vasc Bras. 2021;20:e20200230.
17. Zhang R, Sun L, Sun W, Yang S, Hao Y. Endovascular repair of penetrating aortic ulcers: indications and single-center midterm results. Ann Vasc Surg. 2022;81:129–37.
18. Sensi L, Pisano E, Magnoni F, Pilato A, Pedrini L. Endovascular and surgical repair for penetrating ulcers of the abdominal aorta. Ital J Vasc Endovasc. 2006;13(2):87–93.
19. Fyntanidou B, Massa E, Papachristodoulou A, Karatziou C, Karatziou H, Megalopoulos A, et al. Endovascular repair of infrarenal abdominal aorta penetrating atherosclerotic ulcers: review of our experience. Eur J Vasc Endovasc Surg. 2008; 36(6):746.
20. Lomazzi C, Piffaretti G, D'Oria M, Benedetto F, Stilo F, Mezzetto L, et al. Early and midterm results after endovascular repair of non-infected saccular lesions of the infrarenal aorta. Eur J Vasc Endovasc Surg. 2022;63(6):808–16.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344–9.

22. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg. 2002;35(5):1048–60.
23. R Core Team. R: A language and environment for statistical computing [computer software]. Vienna: R Foundatoin for Statistical Computing; 2022.
24. Bianchini Massoni C, Ancetti S, Perini P, Spath P, D'Ospina RM, Gallitto E, et al. Infrarenal EVAR for penetrating aortic ulcer: a comparative study with abdominal aortic aneurysm. Ann Vasc Surg. 2023;88:327–36.
25. Schmitz-Rixen T, Steffen M, Böckler D, Grundmann RT. Versorgung des abdominellen Aortenaneurysmas (AAA) 2019. Gefässchirurgie. 2021;26(1):41–8.

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ORCID
Johannes Hatzl
https://orcid.org/0000-0002-3152-7791
Christian-Alexander Behrendt
https://orcid.org/0000-0003-0406-3319
Thomas Schmitz-Rixen
https://orcid.org/0000-0002-6082-0006

Correspondence address
Dr. med. Johannes Hatzl
Department of Vascular and Endovascular Surgery
University Hospital Heidelberg
Im Neuenheimer Feld 420
69120 Heideberg
Germany

johannes.hatzl@web.de

Original communication

Meta-analysis and meta-regression of the total endovascular aortic repair in aortic arch

Wael Ahmad, Moritz Wegner[a], and Bernhard Dorweiler[a]

Department of Vascular and Endovascular Surgery-University of Cologne, Faculty of Medicine and University Hospital Cologne, Germany
[a]Both authors share the last authorship.

Summary: *Background:* The total endovascular repair of the aortic arch is becoming more and more an acceptable alternative to the open repair in selected patients. The aim of the present study is to perform a meta-analysis of the available data on the outcomes of the various endovascular techniques used to treat the pathologies in this challenging anatomical area. *Patients and methods:* An extensive electronic search in PubMed/MEDLINE, Science Direct Databases, and the Cochrane Library was conducted. All papers published up to January 2022 on the endovascular techniques in the aortic arch (chimney-thoracic endovascular aortic repair (ChTEVAR), fenestrated/branched grafts as custom made devices (CMD) and surgeon modified TEVAR (SM TEVAR) providing information about at least one of the essential outcomes defined in the inclusion criteria. *Results:* Out of the 5078 studies found through the search in the databases and registers, 26 studies with a total number of patients of 2327 with 3497 target vessels were included in the analysis. The studies reported a high technical success rate with an estimated proportion of 95.8% (95% CI, 93–97.6%). Moreover, the pooled estimation of the early type Ia/III endoleak was 8.1% (95% CI, 5.4–12.1%). The pooled mortality was 4.6% (95 CI, 3.2–6.6%) with a significant heterogeneity and the stroke had an estimated proportion (major and minor combined) of 4.8% (95% CI, 3.5–6.6%). A meta-regression analysis showed no significant variation between the groups in mortality (P=.324) showed however a significant difference between the therapeutic methods regarding stroke P<.001 (lower rate in ChTEVAR and SM vs. CMD). *Conclusions:* The present meta-analysis could demonstrate good short- and long-term outcomes of the multiple total endovascular repair methods used in the aortic arch.

Keywords: Aortic dissection, thoracic aorta, thoracic endovascular aortic repair, aneurysm, stroke

Introduction

As an alternative to the open repair, especially in patients who are assessed to be unfit for surgery the endovascular repair opened the door for treating aortic arch pathologies with encouraging results [1, 2].

The implementation of the endovascular procedures in this anatomical challenging zone paved the road for the development of several endovascular techniques like chimney (or parallel stents, snorkel, periscopes...) thoracic endovascular aortic repair (ChTEVAR), fenestrated/branched stent-grafts as custom made devices (CMD), surgeon modified TEVAR (SM TEVAR or back-table physician-modified grafts) and in situ fenestration.

However, the relatively small sample size of the published studies on the beforementioned procedures and the limited available outcome analysis of these procedures done in landing zone 0 and 1 beyond the left subclavia artery drove us to perform a dedicated review and meta-analysis of the available data. Moreover, we performed a regression analysis (meta-regression) to comparing the outcomes of these different endovascular methods.

Since the in situ-fenestration procedure has been extensively discussed in two recent reviews [3, 4], we decided not to include the studies describing this method in our review. However, we will discuss the in-situ fenestration in the light of the results of these review articles.

Methods

Search strategy (review protocol)

This review of the current data on the endovascular repair procedures of aortic arch (including chimney/snorkel technique, fenestrated and branched custom-made devices and surgeon modified devices) diseases was performed according to "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews" [5].

We conducted an extensive search in PubMed/MEDLINE, Science Direct Databases, and the Cochrane Library. The search included all papers published up to January 2022 in any language. Medical Subject Headings terms

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used included "aortic arch," "chimney stent grafts", "chimney graft", "chimney", "periscope", "snorkel", "fenestrated", branched", "custom made", "surgeon modified", "physician modified", "thoracic", "arch", "thoracic aorta", "endovascular repair", "TEVAR." We looked also in the reference list of the retrieved studies for relevant articles. The review is registered in the International prospective register of systematic reviews (PROSPERO) under the ID: CRD42022367109.

Eligibility and inclusion criteria

A study was considered eligible according to the following inclusion criteria:

(1) Describing an endovascular repair of the arch using chimney, fenestrated/branched (custom-made devices) or surgeon modified stent graft with or without adjunct extra-anatomic debranching.
(2) Reporting of a case series of $\geq$10 patients in whom the brachiocephalic artery and/or the left common carotid artery was/were target vessels for the endovascular repair.
(3) Providing information about at least one of the essential outcomes: early and late type I/III endoleak, 30-day mortality rate, early and late patency, incidence of perioperative stroke, re-intervention and retrograde aortic dissection.

Exclusion criteria

(1) Case reports or case series with <10 patients.
(2) Technical notes or case series without describing relevant outcomes.
(3) Experimental works (in-vitro or ex-vivo).

Study selection

Articles were selected at the title and abstract level, and the selected papers were critically evaluated for eligibility before inclusion. Articles were excluded if they did not describe the type of the used technique and at least one of the basic outcomes or if the data were not original. Only the most recent report from each center was analyzed in case of duplicate publications on the same population of patients (Figure 1).

Data extraction

Two reviewers have independently extracted the following data from each study: Number of patients, number of target vessels, landing zones urgency of treatment, type of aortic lesion treated, type of stent grafts or stents used, technical success (defined as successful deployment of the main stent graft as well as the bridging stents/chimney grafts with complete exclusion of the aortic arch disease and without any type I or III endoleak on completion angiography), median length of follow-up, early and late patency, early and late type I /III endoleak, mortality rates, complications (retrograde A dissection), development of perioperative stroke and spinal cord ischemia.

Early patency and early endoleaks were defined as those identified during the first 30 postoperative days.

Outcomes

Primary outcomes were technical success, 30-day mortality, type I/III endoleak, stroke and spinal cord ischemia.

The secondary outcomes were the mortality, reintervention and patency during the follow-up.

Statistical analysis

Continuous variables were reported as median with quartiles (25% and 75%) or mean±standard deviation. The pooled proportions of event rates of the significant outcomes were calculated using the Freeman-Tukey transformation (arcsine square root transformation) to calculate the weighted summary proportion under the random-effects model (DerSimonian and Laird) [6]. Forest plot graphs were used to illustrate the weighted outcomes as well as the pooled estimation with the 95% confidence interval (CI).

We used the Cochran Q and I^2 tests to assess the heterogeneity. Cochrane Q was calculated, and $P<.05$ was used to indicate the presence of heterogeneity. An I^2 value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity (I^2 between 30% and 60% indicates a moderate heterogeneity, >60% indicates substantial heterogeneity, and >75% indicates considerable heterogeneity).

Because of the design of this meta-analysis including single arm studies only, we assessed the bias of the eligible studies using the Egger regression analysis [7] (we considered P value <.05 significant with one-sided Egger test).

Additionally, we performed a meta-regression analysis (random-effect meta-regression) to compare the outcomes of the different studies while adjusting for the effect of the used therapy method. We considered a $P<.05$ as significant for the meta-regression.

The statistical analysis was performed using the Comprehensive Meta-Analysis Package V3 (Biostat, Englewood, NJ) statistical software.

Results

"Studies" characteristics

We have identified 5078 studies through the search in the databases and registers. After screening and assessment of

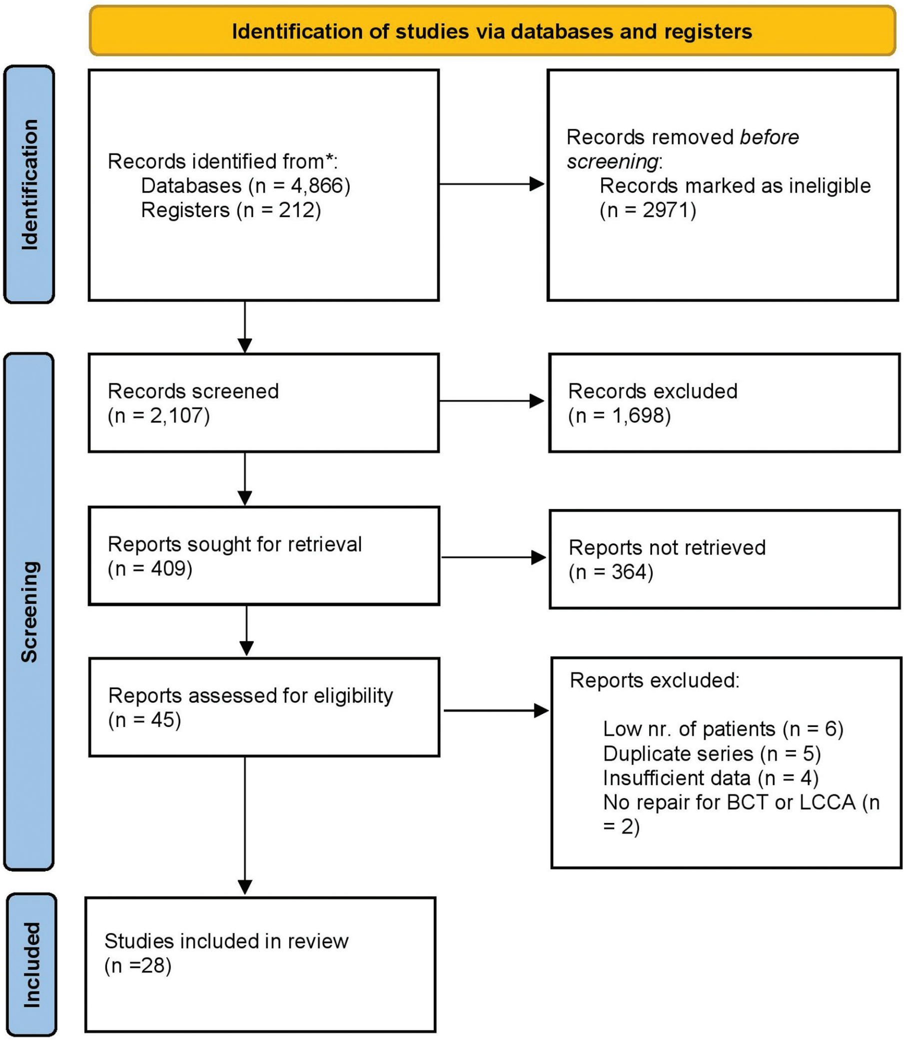

Figure 1. Flow-chart of the search method.

the records, only 45 reports were identified as "eligible" for the analysis. Eventually, 26 studies [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34] with a total number of patients of 2327 with 3497 target vessels were included in the analysis (Figure 1). The number of patients varied between the studies regarding the operative method: 916 (39%) had ChTEVAR, 559 (24%) had CMD (fenestrated or branched) and 852 (37%) had SM-TEVAR.

The patients included in the analyzed studies were treated due to aortic dissection in 50% of cases, 37% aneurysms, 7% penetrating aortic ulcers, 2% intra mural hematoma, 2% pseudo-aneurysms and 2% due to endoleak Ia or traumatic aortic injury. Significantly more patients with aneurysm were treated with CMD and more dissections were managed with ChTEVAR or SM TEVAR (both P<.001).

The details of the included studies and the outcomes are summarized in Tables I and II.

The proximal landing zone was 0 in 12%, 84%, 21% and I in 23%, 12%, 15% and II in 65%, 4% and 64% in the ChTEVAR, CMD and SM TEVAR groups respectively.

The results of the meta-analysis demonstrated as an estimated pooled proportion stratified according to the used procedure as well as the heterogeneity and bias are shown in Table III.

Operative outcomes with meta-analysis

The studies reported a relatively high technical success rate between 84% and 100%. An exception was this reported by Dueppers et al. [13] with 37%. The overall estimated proportion of technical success for all procedures together reached 95.8% (95% CI: 93–97.6%) (Figure 2). Both the bias (P>.001) and heterogeneity between studies (Q. P<.001; I^2=80.8%) were significant.

Moreover, the pooled estimation of the early type Ia/III endoleak was 8.1% (95% CI: 5.4–12.1%) but with a significant publication bias and heterogeneity (Q. P<.0001; I^2=82% and P=.032, respectively) (Figure 3).

Regarding 30-day mortality, the overall estimated proportion was 4.6% (95% CI: 3.2–6.6%) with a significant heterogeneity (Q. P<.001; I^2=58%) but not the bias (P=.084). However, the mortality as reported in the

Table I. Details of the included studies

Study	Year	Patients	Technique	Nr. of TV	LZ 0	LZ 1	LZ 2	LZ 3
Tenorio et al. [28]	2021	39	BTEVAR	117	39	0	0	0
Verscheure et al. [31]	2021	70	BTEVAR	147	70	0	0	0
Kudo et al. [18]	2020	28	BTEVAR	52	28	0	0	0
Tsilimparis et al. [29]	2019	54	BTEVAR	108	54	0	0	0
Clough et al. [12]	2018	30	BTEVAR	N/A	30	0	0	0
Lu et al. [24]	2015	51	BTEVAR	90	33	0	18	0
Haulon et al. [15]	2014	38	BTEVAR	76	38	0	0	0
Dueppers et al. [13]	2021	33	ChTEVAR	48	4	5	24	0
Ahmad et al. [8]	2020	54	ChTEVAR	91	39	13	2	0
Shu et al. [27]	2020	126	ChTEVAR	158	9	32	85	0
Zhang et al. [33]	2020	364	ChTEVAR	518	21	112	231	N/A
Huang et al. [16]	2019	226	ChTEVAR	230	22	13	191	0
Bosiers et al. [9]	2016	95	ChTEVAR	102	13	24	63	N/A
O'Callaghan et al. [25]	2014	18	ChTEVAR	18	1	16	1	0
Li et al. [22]	2021	16	F/BTEVAR	39	16	0	0	0
Fernández-Alonso et al. [14]	2020	14	FTEVAR	15	6	8	0	0
Sato et al. [26]	2020	37	FTEVAR	N/A	31 (1 pat. missing)	5 (1 pat. missing)	0	0
Tsilimparis et al. [30]	2020	44	FTEVAR	73	12	27	5	0
Yuri et al. [32]	2017	54	FTEVAR	N/A	51	3	0	0
Iwakoshi et al. [17]	2015	32	FTEVAR	71	30	2	0	0
Kurimoto et al. [20, 24]	2015	37	FTEVAR	74	37	0	0	0
O'Callaghan et al. [25]	2014	15	FTEVAR	15	1	13	1	0
Li et al. [21]	2021	513	SM FTEVAR	626	54	77	382	N/A
Chassin-Trubert [11]	2021	50	SM FTEVAR	100	49	1	0	0
Li et al. [23]	2021	37	SM FTEVAR	104	37	0	0	0
Shu et al. [27]	2020	102	SM FTEVAR	113	1	7	93	1
Zhang et al. [33]	2020	110	SM FTEVAR	165	10	35	65	N/A
Canaud et al. [10]	2019	17	SM FTEVAR	34	17	0	0	0
Kuo et al. [19]	2019	13	SM FTEVAR	38	13	0	0	0
Zhu et al. [34]	2018	10	SM FTEVAR	22	5	5	0	0

Notes. Nr. of TV: number of target vessels; LZ: landing zone; ChTEVAR: chimney-thoracic endovascular aortic repair; FTEVAR: fenestrated TEVAR; BTEVAR: branched-TEVAR; SM-TEVAR: surgeon-modified TEVAR.

analyzed studies varied between 0% and 18.5% (Electronic supplementary material [ESM] 1).

Another important outcome here is the periprocedural stroke. We found an estimated proportion of the stroke (major and minor combined) of 4.8% (95% CI: 3.5–6.6%). Similar to "mortality" the bias was not significant (P=.358) and the heterogeneity was (Q. P .001; I^2=50%) (ESM 2). The spinal cord ischemia (SCI) has an estimated rate of 2% (95% CI: 1.4–2.8%) without significant heterogeneity (Q. P=.67; I^2=0%) or bias (P=.126).

Furthermore, the in the meta-analysis included studies reported a 0.9% event rate of retrograde type A aortic dissection (rAAD) as a complication resulting in a pooled estimation of 1.9% (95% CI: 1.3–2.7%) without a significant heterogeneity (Q. P=.831; I^2=0%) or publication bias (P=.279) (ESM 3).

The re-interventions were required in 237 patients (10.2%) yielding a pooled estimated rate of 11.4% (95% CI: 7.8–16.4%) with a significant heterogeneity (Q. P<.001; I^2=85%) and bias (P=.031) (ESM 4).

Interestingly a high rate of patency was reported during follow-up (all the studies but one [26] provided information) with an estimated event rate of 97.6% (95% CI: 95.8–98.7%). However, publication bias (P<.001) and heterogeneity (Q. P<.001; I^2=67%) were both significant.

Meta-regression

A meta-regression analysis using the endovascular methods as moderators and the CMD as a reference group showed no significant variation between the groups in mortality (P=.324) or the rAAD (P=.219), showed however a significant difference between the therapeutic methods regarding stroke P<.001 (lower rate in ChTEVAR and SM vs. CMD). Similarly, the SCI was significantly more frequent in the CMD group compared to SM TEVAR group (P=.007) and showed a tendency to have a higher rate compared to ChTEVAR (P=.06).

Regarding endoleak, the SM and CMD groups have significantly lower endoleak rate than ChTEVAR group

Table II. The operative and follow-up outcomes of the eligible studies

Study	Year	Technique	Elective	Emergency	Technical success	Post. OP EL I/III	30-day mortality	Aortic related	Stroke	Paraplegia	rTAAD
Tenorio et al. [28]	2021	BTEVAR	39/100%	0/0%	100%	3/7.7%	2/5.1%	0/0%	2/5.1% (one minor)	0/0%	0/0%
Verscheure et al. [31]	2021	BTEVAR	70/100%	0/0%	94.30%	1/1.4%	2/2.9%	0/0%	2/2.9%	0/0%	0/0%
Kudo et al. [18]	2020	BTEVAR	28/100%	0/0%	100%	0/0%	0/0%	0/0%	4/14.3% (2/7.1% transient)	0/0%	0/0%
Tsilimparis et al. [29]	2019	BTEVAR	43/80%	11/20%	98%	1/1.9%	3/5.6%	N/A	6/11.1% (3/5.6% minor)	3/5.6% (1/1.9% immediate full 2/3.7% delayed partial)	0/0%
Clough et al. [12]	2018	BTEVAR	30/100%	0/0%	90%	4/13.3%	3/10%	0/0%	1/3.3%+1/3.3% TIA	0/0%	0/0%
Lu et al. [24]	2015	BTEVAR	51/100%	0/0%	100%	0/0%	1/2.0%	1/2.0%	0/0%	0/0%	1/2.0%
Haulon et al. [15]	2014	BTEVAR	38/100%	0/0%	84.2%	6/15.8%	5/13.2%	1/2.6%	5/13.2% (1/2.6% TIA)	1/2.6%	0/0%
Li et al. [22]	2021	F/BTEVAR	16/100%	0/0%	100%	0/0%	1/6.25%	1/6.25%	1/6.25%	0/0%	1/6.25%
Fernández-Alonso et al. [14]	2020	FTEVAR	14/100%	0/0%	100%	0/0%	1/7.1%	0/0%	1/7.1%	0/0%	0/0%
Sato et al. [26]	2020	FTEVAR	37/100%	0/0%	97.30%	10/27.8%	0/0%	0/0%	6/16.2%	1/2.7%	N/A
Tsilimparis et al. [30]	2020	FTEVAR	41/93%	3/7%	95%	7/15.9%	4/9.1%	1/2.3%	4/9.1% (1/2.3% minor)	0/0%	1/2.3%
Yuri et al. [32]	2017	FTEVAR	54/100%	0/0%	100%	1/1.9%	2/2.7%	0/0%	1/1.9%	1/1.9% (transient)	0/0%
Iwakoshi et al. [17]	2015	FTEVAR	32/100%	0/0%	91%	3/9.4%	0/0%	0/0%	1/3.1%	1/3.1%	2/6.3%
Kurimoto et al. [20, 24]	2015	FTEVAR	36/97.3%	1/2.7%	100%	12/32.4%	0/0%	0/0%	2/5.4%	2/5.4%	0/0%
O'Callaghan et al. [25]	2014	FTEVAR	15/100%	0/0%	93.3%	0/0%	1/6.7%	0/0%	1/6.7%	1/6.7%	1/6.7%
Dueppers et al. [13]	2021	ChTEVAR	25/76%	8/24%	37%	26/78.8%	3/9%	1/3%	2/6%	1/3% (transient)	1/3%
Ahmad et al. [8]	2020	ChTEVAR	42/77.8%	12/22.2%	98%	8/14.5%	10/18.5%	4/7.4%	6/11.1%	2/3.7%	3/5.6%
Shu et al. [27]	2020	ChTEVAR	56/44.4%	70/55.6%	100%	14/11.1%	3/2.4%	0/0%	2/1.6%	0/0%	2/1.6%
Zhang et al. [33]	2020	ChTEVAR	347/95.3%	17/4.7%	100%	39/10.7%	3/0.8%	1/0.3%	8/2.2% (7/1.9% TIA)	1/0.3%	1/0.3%
Huang et al. [16]	2019	ChTEVAR	216/95.6%	10/4.4%	84%	37/16.4%	4/1.8%	1/0.4%	4/1.8%	3/1.3% (1/0.4% temporary)	0/0%
Bosiers et al. [9]	2016	ChTEVAR	49/51.6%	46/48.4%	89.5%	10/10.5%	9/9.5%	2/2.1%	2/2.1%	1/1.1%	1/1.1%
O'Callaghan et al. [25]	2014	ChTEVAR	11/61.1%	7/38.9%	100%	1/5.6%	3/16.7%	0/0%	1/5.6%	1/5.6%	0/0%
Li et al. [21]	2021	SM FEVAR	479/93.4%	34/6.6%	98.6%	0.6%	13/2.5%	2/0.4%	12/2.3%	2/0.4%	6/1.2%
Zhang et al. [33]	2020	SM FEVAR	107/97.2%	3/2.8%	100%	1/0.9%	1/0.9%	1/0.9%	1/0.9% (TIA)	0/0%	1/0.9%
Chassin-Trubert [11]	2021	SM FTEVAR	38/76%	12/24%	94%	1/2%	1/2%	0/0%	2/4% (minor)	0/0%	0/0%
Li et al. [23]	2021	SM FTEVAR	N/A	N/A	91.90%	0/0%	2/5.4%	0/0%	2/5.4%	0/0%	0/0%
Shu et al. [27]	2020	SM FTEVAR	60/58.8%	42/41.2%	99%	1/1.0%	2/2.0%	0/0%	2/2.0%	0/0%	0/0%
Canaud et al. [10]	2019	SM FTEVAR	15/88.2%	2/11.8%	100%	0/0%	0/0%	0/0%	1/5.9%	0/0%	0/0%
Kuo et al. [19]	2019	SM FTEVAR	10/76.9%	3/23.1%	100%	0/0%	0/0%	0/0%	0/0%	0/0%	0/0%
Zhu et al. [34]	2018	SM FTEVAR	8/80%	2/20%	90%	0/0%	1/10%	0/0%	0/0%	0/0%	1/10%

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Table II. (Continued)

Study	Year	Technique	Early patency	Follow-up (months)	Re-intervention	Late patency	Mortality	Aortic related	New EL I
Tenorio et al. [28]	2021	BTEVAR	95%	3.2 (IQR: 1–14)	14/35.9%	91%	2/5.1%	0/0%	0/0%
Verscheure et al. [31]	2021	BTEVAR	100%	10 (range: 4.6–21.4)	32/45.7%	100%	8/11.4%	1/1.4% possible	3/4.3%
Kudo et al. [18]	2020	BTEVAR	100%	48±24 (IQR: 6–84)	2/7.1%	100%	5/17.9%	1/3.6%	0/0%
Tsilimparis et al. [29]	2019	BTEVAR	100%	12±9	3/5.6%	98%±2%	4/7.4%	1/1.9%	0/0%
Clough et al. [12]	2018	BTEVAR	100%	12.0 (range: 1.0–67.8)	6/20.0%	N/A	6/20.0%	0/0%	1/3.3%
Lu et al. [24]	2015	BTEVAR	100%	44 (range:. 14–66)	0/0%	100%	0/0%	0/0%	0/0%
Haulon et al. [15]	2014	BTEVAR	100%	12 (range: 6–12)	3/7.9%	100%	4/10.5%	0/0%	0/0%
Li et al. [22]	2021	F/BTEVAR	100%	98 (range:. 0–119)	2/12.5%	87.5%	4/25%	1/6.26%	0/0%
Fernández-Alonso et al. [14]	2020	FTEVAR	100%	37.5 (3–72)	2/14.3%	100%	0/0%	0/0%	1/7.1%
Sato et al. [26]	2020	FTEVAR	N/A	34.8±34.8	3/8.1%	N/A	4/10.8%	1/2.7%	0/0%
Tsilimparis et al. [30]	2020	FTEVAR	100%	18±17	3/6.8%	98%	N/A	2/4.5%	0/0%
Yuri et al. [32]	2017	FTEVAR	100%	41.4±26 (range: 1.6–97.7)	4/7.4%	100%	13/24.1%	0/0%	1/1.9%
Iwakoshi et al. [17]	2015	FTEVAR	97%	30 (range: 2.4–74.4)	4/12.5%	97%	0/0%	1/3.1%	0/0%
Kurimoto et al. [20, 24]	2015	FTEVAR	100%	16.9±12.8 (range: 1–63)	6/16.2%	N/A	6/16.2%	0/0%	0/0%
O'Callaghan et al. [25]	2014	FTEVAR	93.30%	13.5 (min–max: 1–50)	4/26.7%	93.3%	2/13.3%	0/0%	1/6.7%
Dueppers et al. [13]	2021	ChTEVAR	91%	48±31	14/42.4%	N/A	16/49%	N/A	N/A
Ahmad et al. [8]	2020	ChTEVAR	98%	20±25	5/9.3%	97.8%	N/A	1/1.9%	N/A
Shu et al. [27]	2020	ChTEVAR	100%	27 (range: 19–39)	5/4.0%	100%	10/7.9%	N/A	0/0%
Zhang et al. [33]	2020	ChTEVAR	N/A	50.9±20.6	67/18.4%	83%	39/10.7%	8/2.2%	39/10.7%
Huang et al. [16]	2019	ChTEVAR	100%	22±16	1/0.4%	97.4%	5/2.2%	3/1.3%	2/0.8%
Bosiers et al. [9]	2016	ChTEVAR	98%	60	N/A	88.6%	N/A	N/A	NA
O'Callaghan et al. [25]	2014	ChTEVAR	100%	22.2 (min–max: 1–85)	6/33.3%	88.9%	0/0%	0/0%	1/5.6%
Li et al. [21]	2021	SM FEVAR	99.40%	27 (IQR: 13–31)	18/3.5%	99.6%	12/2.3%	5/1.0%	15/2.9%+2/0.4% III
Zhang et al. [33]	2020	SM FEVAR	N/A	49.5±18.3	3/2.7%	92%	12/10.9%	3/2.7%	1/0.9%
Chassin-Trubert [11]	2021	SM FTEVAR	100%	16±8.3	4/8%	100%	2/4%	0/0%	0/0%
Li et al. [23]	2021	SM FTEVAR	100%	20 (range: 3–49)	5/13.55	97%	5/13.5%	2/5.4%	N/A
Shu et al. [27]	2020	SM FTEVAR	100%	28 (range: 20–41)	0/0%	99%	5/4.9%	N/A	0/0%
Canaud et al. [10]	2019	SM FTEVAR	100%	7±2	3/17.6%	100%	0/0%	0/0%	0/0%
Kuo et al. [19]	2019	SM FTEVAR	100%	23 (range: 3–28)	6/46.2%	100%	3/23.1%	2/15.4%	0/0%
Zhu et al. [34]	2018	SM FTEVAR	100%	13.3 (range: 6.0–19.0)	1/10%	100%	0/0%	0/0%	0/0%

Notes. El: endoleak; BCA: brachiocephalic artery; LCCA: left common carotid artery; LSA: left subclavian artery; rTAAD: retrograde type A aortic dissection; IQR: interquartile range.

Table III. The results of the meta-analysis and the assessment of heterogeneity (Cochrane-Q and I^2 tests) and the bias (Egger's test) in the studies according to different outcomes

Outcome*	ChTEVAR	Egger (P)	Q-test (P)	I^2	CMD	Egger (P)	Q-test (P)	I^2	SM-TEVAR	Egger (P)	Q-test (P)	I^2
Technical success	93.9% (81–98%)	.184	<.001	90.7%	94.5% (91.4–96.5%)	<.001	.259	17%	96.9% (93.5–98.6%)	.381	.066	47%
PostOP endoleak I/III	17.5% (9.5–29.8%)	.27	<.001	90%	8.5% (4.8–14.5%)	<.001	<.001	66%	2.8% (1.9–4.3%)	.068	.837	0%
30-day mortality	5.4% (2.2–12.7%)	.108	<.001	84.9%	6% (4.2–8.7%)	<.001	.595	0%	2.7% (1.8–4.1%)	.361	.741	0%
Stroke	3.4% (1.7–6.4%)	.493	.024	58.6%	8.4% (6–11.5%)	<.001	.351	9%	2.7% (1.8–4.1%)	.212	.805	0%
Spinal cord ischemia	1.6% (0.07–3.3%)	.304	.251	23%	3.1% (1.8–5.1%)	<.001	.971	0%	0.9% (0.4–2%)	<.001	.682	0%
Retro. A dissection	1.5% (0.6–3.8%)	.067	.111	42%	2.5% (1.4–4.5%)	.001	.95	0	1.5% (0.8–2.6%)	.263	.6	0
Re-intervention	11.5% (5.5–22.5%)	.161	.001	88%	13.4% (81–21.4%)	<.001	<.001	78%	8.4% (3.5–18.7%)	.23	<.001	82%
Primary patency	97.9% (92.8–99.4%)	.002	.001	73%	97.6% (95.5–98.7%)	<.001	.95	0%	97.2% (89.5–99.3%)	.066	.001	85%

Notes. *The outcomes reported as an estimated pooled proportion with 95% CI (confidence interval).

(P<.001 and P=.04, respectively). Moreover, the SM group had less endoleak than the CMD (P=.007). Furthermore, all three methods showed no significant difference in re-intervention rate during follow-up (P=.621).

Discussion

The present meta-analysis offers a summary with a detailed analysis of the up to date published data regarding the endovascular procedures the most used in the aortic arch focusing on the feasibility, safety and the operative outcomes.

In this analysis, we included only studies with at least 10 patients in whom two or more supra aortic vessels were endovascularly vascularized. The reason for this decision was the complexity and the frequent periprocedural complications of endovascular repair in zones 1 and 0 compared to more distal, proximal landing zones.

We found a high technical success estimated rate ≥94% throughout all the three procedural types (Table III). However, a significant heterogeneity in ChTEVAR group and publication bias in the CMD group were detected.

Despite the wide variation of the reported 30-day mortality in the analyzed studies between 0% and 18.5%, the estimated proportion was low with 4.6% (95% CI: 3.2–6.6%) particularly when compared to this reported by Liakopoulos et al. in their experience with frozen elephant truck (FET) in treating aortic arch diseases (11.1% for non-acute A dissections) [35] and to the mortality rate (8.8%) described in a large review of FET with over 3000 patients [36].

Other important outcomes, the periprocedural stroke and the SCI were estimated to be 4.8% (95% CI: 3.5–6.6%) and 2% (95% CI: 1.4–2.8%) respectively, in all procedures combined. These rates are clearly lower than the prevalence of stroke and SCI varying between 8.8–15.2% and 5.6–8.8% reported in most FET series [35, 37, 38]. However, a meta-analysis of arch hybrid repair and open repair from 2013 showed a lower prevalence of stroke with 7.6% and 6.2%, respectively [39].

Although the SM TEVAR and CHTEVAR showed in the meta-regression better stroke rate than the CMD, we should mention that the proximal landing zones 0 and I were clearly more frequent in the CMD compared to the ChTEVAR (35%) and SM TEVAR (36%) groups (ESM 5), and this in turn can explain the higher calculated stroke rate in the CMD group [40].

Although the stroke rates in all groups were lower than that reported in the standard TEVAR [41], the cerebrovascular accidents still a major challenge of the aortic arch endovascular repair due to the risk of atherosclerotic and gaseous embolization. Thus, some authors recommend the temporary clamping of the carotid arteries during manipulation/deployment of the stent graft and to flush the devices with CO_2 before saline to reduce the air trapped in the graft [29, 42].

Interestingly, the SCI was also higher in the CMD group with an incidence of >5% reported in three series;

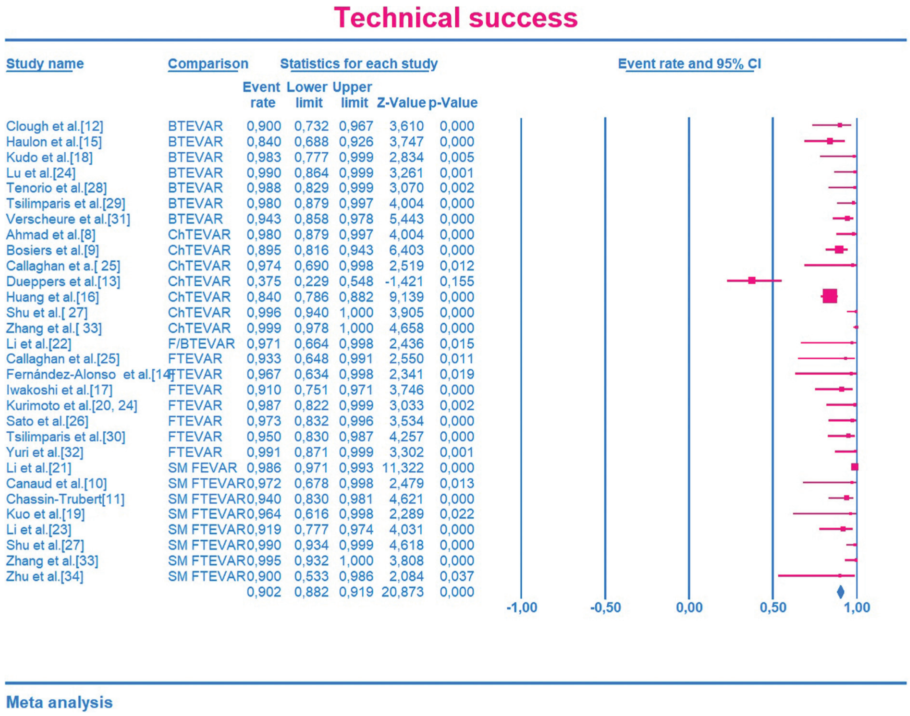

Figure 2. Forest plot of the overall estimated proportion of technical success.

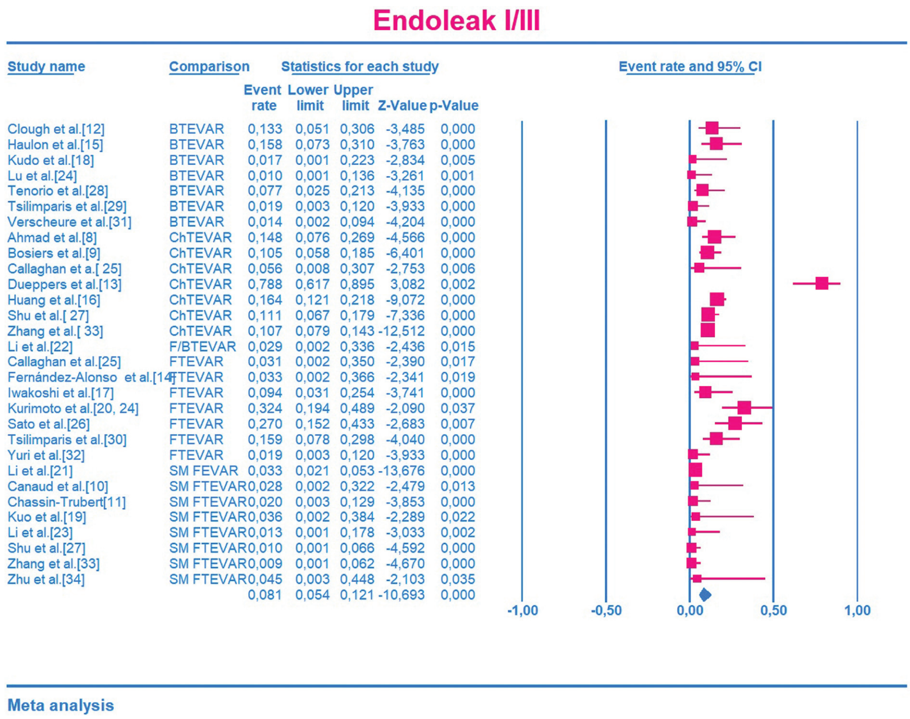

Figure 3. Forest plot of the overall estimated proportion of perioperative endoleak type I/III.

Tsilimparis et al. [29] reported a 5.6% rate with one case of permanent and two of temporary paraplegia without providing more information about the length of aortic covering, the use of spinal drainage or subclavian reconstruction. Kurimoto et al. [20] reported SCI in 3 patients (5.4%), in whom the distal end of the stent graft was at the level of Th 10, 8 and 6, one with a covered, not reconstructed left subclavian artery and two with occluded iliac arteries. An even higher rate (6.7% – only one patient) was mentioned by O'Callaghan et al. [25]. This patient developed lower limb weakness after removal of the spinal drainage and recovered after reinserting it. In the same study, the authors reported a 5.6% SCI between the 18 patients who received ChTEVAR. The covered subclavia artery in the patient who developed the ischemia was not reconstructed due to the urgency of case and without improvement after the delayed revascularization.

From the systematic analysis of Prendes et al. [4] only one study [43] met the inclusion criteria we used for this meta-analysis. In this study, 148 patients with 183 arch vessels were treated with in-situ laser fenestration of a thoracic stent-graft (using 980-nm laser system calibrated to deliver pulses at 18 W of energy in 3 seconds) due to aortic arch pathologies with 97.3% technical success.

The reported 30-day mortality was 2.9% with a stroke rate of 5% similar to the estimated pool proportion of our study groups.

There were seven endoleaks (4.7%: one type Ib, three type IIIC, and three type II), three retrograde dissections (2.0%), and five strokes (3.4%). No branch stent graft occlusion or spinal ischemia was reported.

To provide a comparative overview of the 3 methods we analyzed we performed a meta-regression analysis. This analysis showed a significant higher rate of endoleak Type I/III than SM TEVAR and CMD despite the significant heterogeneity of the ChTEVAR studies (Q. $P<.001$; $I^2=90\%$). The reported endoleak in the ChTEVAR series ranged between 5.6% [25] and 16.4% [16] except for the very high 78.8% endoleak rate reported by Dueppers et al. [13]. However, in this study (included 33 patients) no standardized method was used; chimneys, periscopes, sandwich and debranching with different target vessels, proximal neck lengths and diverse lengths of bridging stents. To reduce the incidence of gutter endoleaks in ChTEVAR a sealing zone distal to the last chimney graft of more than 10 mm was suggested [44].

The re-intervention was frequently needed in 11.4% (pooled) of patients but not significantly varied between the different methods used: ChTEVAR 11.5%, CMD 13.4% and SM TEVAR 8.4%.

Reasons for re-intervention were new endoleaks, stent graft migration, stent induced new entry (SINE), bridging stents occlusion, aneurysmal degeneration and new false lumen formation.

Although the re-intervention seemed to be relatively frequent, the reported patency during follow up was remarkably high; ≈98% as a pool estimation in ChTEVAR and CMD groups (with a significant publication bias) and 97% in the SM TEVAR group.

The most feared complication in the aortic arch is the rAAD. Fortunately, the incidence of this catastrophic complication still low with a pooled estimation of 2%. However, higher incidences (5.6–6.7%) were reported in several works [8, 17, 22, 25]. To reduce the incidence of the rAAD in TEVAR procedures; avoidance of post-ballooning, abstain from the use of stent grafts with proximal bare springs and from the excessive oversizing of the aortic stent grafts especially in patients with type B aortic dissection were suggested [45, 46].

Finally, although the CMDs (as fenestrated or branched) are going to be more and more implemented in the treatment of arch pathologies, the long time required for their production limits their use in the urgent situation. Therefore, the SM TEVAR and ChTEVAR still find their place in the endovascular armamentarium with acceptable outcomes, may be until an off-the-shelf fenestrated/branched device is available.

Limitations

An important limitation is the absence of data directly comparing the different endovascular methods in the aortic arch in term of a case-control study due to the nature of the patients and the pathologies treated using the endovascular method as an alternative to open repair.

Similarly, direct comparison between endovascular and open repair does not exist. Being applied mostly in older patients suffering from severe comorbidities and frailty, long-term results of endovascular repair of the aortic arch are lacking and against this background, favorable outcomes of open repair seem somehow unsurprising.

Moreover, the significant heterogeneity and bias seen in many outcomes of the reviewed study reduces the robustness of the reported outcomes.

Conclusions

The present meta-analysis could demonstrate acceptable short- and long-term outcomes of the multiple total endovascular repair methods (ChTEVAR, SM TEVAR and CMD) used in the aortic arch. Despite the higher stroke rate seen in the CMD groups, this method was used mainly in zone 0 and 1 compared to the other methods. The ChTEVAR had significantly more perioperative endoleaks.

However, the study is limited by the heterogeneity and publication bias and the absence of studies directly comparing the different methods with each other.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a001061

ESM 1. Forest plot of the overall estimated proportion of mortality. (Figure)

ESM 2. Forest plot of the overall estimated proportion of stroke. (Figure)

ESM 3. Forest plot of the overall estimated proportion of retrograde type A aortic dissection. (Figure)

ESM 4. Forest plot of the overall estimated proportion of reintervention. (Figure)

ESM 5. A diagram showing the landing zones according to the endovascular method. (Figure)

References

1. Czerny M, Schmidli J, Adler S, van den Berg JC, Bertoglio L, Carrel T, et al. Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch: an expert consensus document of the European Association for Cardio-Thoracic surgery (EACTS) and the European Society for Vascular Surgery (ESVS). Eur J Cardiothorac Surg. 2019;55(1):133–62.
2. Ahmad W, Mylonas S, Majd P, Brunkwall JS. A current systematic evaluation and meta-analysis of chimney graft technology in aortic arch diseases. J Vasc Surg. 2017;66(5):1602–10.e2.
3. Li Y, He C, Chen X, Yao J, Zhang T, Zhang H. Endovascular in situ fenestration technique of aortic arch pathology: a systematic review and meta-analysis. Ann Vasc Surg. 2021;76:472–80.
4. Prendes CF, Lindstrom D, Mani K, Tegler G, Wanhainen A. A systematic review of experimental and clinical studies reporting on in situ laser fenestration of aortic endografts. J Vasc Surg. 2022;75(2):740–52.e1.
5. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Esp Cardiol. 2021;74(9):790–9.
6. DerSimonian R, Meta-analysis in the design and monitoring of clinical trials. Stat Med. 1996;15(12):1237–48. discussion 49–52
7. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. BMJ. 2001;323(7304):101–5.
8. Ahmad W, Liakopoulos OJ, Mylonas S, Wegner M, Brunkwall J, Dorweiler B. Long-term outcomes after thoracic endovascular aortic repair using chimney grafts for aortic arch pathologies: 10 years of single-center experience. Ann Vasc Surg. 2021;72:400–8.
9. Bosiers MJ, Donas KP, Mangialardi N, Torsello G, Riambau V, Criado FJ, et al. European Multicenter Registry for the performance of the chimney/snorkel technique in the treatment of aortic arch pathologic conditions. Ann Thorac Surg. 2016;101(6):2224–30.
10. Canaud L, Ozdemir BA, Chassin-Trubert L, Sfeir J, Alric P, Gandet T. Double homemade fenestrated stent graft for total endovascular aortic arch repair. J Vasc Surg. 2019;70(4):1031–8.
11. Chassin-Trubert L, Gandet T, Lounes Y, Ozdemir BA, Alric P, Canaud L. Double fenestrated physician-modified stent-grafts for total aortic arch repair in 50 patients. J Vasc Surg. 2021;73(6):1898–905.e1.
12. Clough RE, Spear R, Van Calster K, Hertault A, Azzaoui R, Sobocinski J, et al. Case series of aortic arch disease treated with branched stent-grafts. Br J Surg. 2018;105(4):358–65.
13. Dueppers P, Reutersberg B, Rancic Z, Messmer F, Menges AL, Meuli L, et al. Long-term results of total endovascular repair of arch-involving aortic pathologies using parallel grafts for supra-aortic debranching. J Vasc Surg. 2022;75(3):813–23.e1.
14. Fernandez-Alonso L, Fernandez Alonso S, Martinez Aguilar E, Santamarta Farina E, Alegret Sole J, Atienza Pascual M, et al. Fenestrated and scalloped endovascular grafts in zone 0 and zone 1 for aortic arch disease. Ann Vasc Surg. 2020;69:360–5.
15. Haulon S, Greenberg RK, Spear R, Eagleton M, Abraham C, Lioupis C, et al. Global experience with an inner branched arch endograft. J Thorac Cardiovasc Surg. 2014;148(4):1709–16.
16. Huang W, Ding H, Jiang M, Liu Y, Huang C, Yang X, et al. Outcomes of chimney technique for aortic arch diseases: a single-center experience with 226 cases. Clin Interv Aging. 2019;14:1829–40.
17. Iwakoshi S, Ichihashi S, Itoh H, Tabayashi N, Sakaguchi S, Yoshida T, et al. Clinical outcomes of thoracic endovascular aneurysm repair using commercially available fenestrated stent graft (Najuta endograft). J Vasc Surg. 2015;62(6):1473–8.
18. Kudo T, Kuratani T, Shimamura K, Sawa Y. Early and midterm results of thoracic endovascular aortic repair using a branched endograft for aortic arch pathologies: a retrospective single-center study. JTCVS Tech. 2020;4:17–25.
19. Kuo HS, Huang JH, Chen JS. Handmade fenestrated stent grafts to preserve all supra-aortic branches in thoracic endovascular aortic repair. J Thorac Cardiovasc Surg. 2020;160(3):629–39.e1.
20. Kurimoto Y, Maruyama R, Ujihira K, Nishioka N, Hasegawa K, Iba Y, et al. Thoracic endovascular aortic repair for challenging aortic arch diseases using fenestrated stent grafts from zone 0. Ann Thorac Surg. 2015;100(1):24–32. discussion 3
21. Li X, Li W, Dai X, Li W, Zhang J, Wang Z, et al. Thoracic endovascular repair for aortic arch pathologies with surgeon modified fenestrated stent grafts: a multicentre retrospective study. Eur J Vasc Endovasc Surg. 2021;62(5):758–66.
22. Li X, Zhang L, Song C, Zhang H, Xia S, Li H, et al. Long-term outcomes of thoracic endovascular repair for aortic arch dissection using customized single-branched fenestrated stent-graft. Vasc Endovasc Surg. 2021;55(6):577–85.
23. Li X, Zhang L, Song C, Zhang H, Xia S, Li H, et al. Outcomes of total endovascular aortic arch repair with surgeon-modified fenestrated stent-grafts on zone 0 landing for aortic arch pathologies. J Endovasc Ther. 2022;29(1):109–16.
24. Lu Q, Feng J, Zhou J, Zhao Z, Li H, Teng Z, et al. Endovascular repair by customized branched stent-graft: a promising treatment for chronic aortic dissection involving the arch branches. J Thorac Cardiovasc Surg. 2015;150(6):1631–8.e5.
25. O'Callaghan A, Mastracci TM, Greenberg RK, Eagleton MJ, Bena J, Kuramochi Y. Outcomes for supra-aortic branch vessel stenting in the treatment of thoracic aortic disease. J Vasc Surg. 2014;60(4):914–20.
26. Sato H, Fukada J, Tamiya Y, Mikami T, Sibata T, Harada R, et al. Long-term clinical outcomes of thoracic endovascular aortic repair for arch aneurysms with the Najuta thoracic stent-graft system. Ann Vasc Dis. 2020;13(4):384–9.
27. Shu C, Fan B, Luo M, Li Q, Fang K, Li M, et al. Endovascular treatment for aortic arch pathologies: chimney, on-the-table fenestration, and in-situ fenestration techniques. J Thorac Dis. 2020;12(4):1437–48.
28. Tenorio ER, Oderich GS, Kolbel T, Dias NV, Sonesson B, Karelis A, et al. Multicenter global early feasibility study to evaluate total endovascular arch repair using three-vessel inner branch stent-grafts for aneurysms and dissections. J Vasc Surg. 2021;74(4):1055–65.e4.
29. Tsilimparis N, Detter C, Law Y, Rohlffs F, Heidemann F, Brickwedel J, et al. Single-center experience with an inner branched arch endograft. J Vasc Surg. 2019;69(4):977–85.e1.
30. Tsilimparis N, Law Y, Rohlffs F, Spanos K, Debus ES, Kolbel T. Fenestrated endovascular repair for diseases involving the aortic arch. J Vasc Surg. 2020;71(5):1464–71.
31. Verscheure D, Haulon S, Tsilimparis N, Resch T, Wanhainen A, Mani K, et al. Endovascular treatment of post type A chronic aortic arch dissection with a branched endograft: early results from a retrospective international multicenter study. Ann Surg. 2021;273(5):997–1003.
32. Yuri K, Kimura N, Hori D, Yamaguchi A, Adachi H. A challenging treatment for aortic arch aneurysm with fenestrated stent graft. Ann Thorac Surg. 2017;104(6):1915–22.
33. Zhang L, Wu MT, Zhu GL, Feng JX, Song C, Li HY, et al. Off-the-shelf devices for treatment of thoracic aortic diseases: midterm follow-up of TEVAR with chimneys or physician-made fenestrations. J Endovasc Ther. 2020;27(1):132–42.
34. Zhu J, Dai X, Noiniyom P, Luo Y, Fan H, Feng Z, et al. Fenestrated thoracic endovascular aortic repair using physician-modified stent grafts (PMSGs) in zone 0 and zone 1 for aortic arch diseases. Cardiovasc Intervent Radiol. 2019;42(1):19–27.
35. Liakopoulos OJ, Kroener A, Sabashnikov A, Zeriouh M, Ahmad W, Choi YH, et al. Single-center experience with the frozen elephant trunk procedure in 111 patients with complex aortic disease. J Thorac Dis. 2020;12(10):5387–97.

36. Poon SS, Tian DH, Yan T, Harrington D, Nawaytou O, Kuduvalli M, et al. Frozen elephant trunk does not increase incidence of paraplegia in patients with acute type A aortic dissection. J Thorac Cardiovasc Surg. 2020;159(4):1189–96.e1.
37. Jakob H, Dohle D, Benedik J, Janosi RA, Schlosser T, Wendt D, et al. Long-term experience with the E-vita Open hybrid graft in complex thoracic aortic diseasedagger. Eur J Cardiothorac Surg. 2017;51(2):329–38.
38. Shrestha M, Martens A, Kaufeld T, Beckmann E, Bertele S, Krueger H, et al. Single-centre experience with the frozen elephant trunk technique in 251 patients over 15 years. Eur J Cardiothorac Surg. 2017;52(5):858–66.
39. Moulakakis KG, Mylonas SN, Markatis F, Kotsis T, Kakisis J, Liapis CD. A systematic review and meta-analysis of hybrid aortic arch replacement. Ann Cardiothorac Surg. 2013;2(3): 247–60.
40. Melissano G, Tshomba Y, Bertoglio L, Rinaldi E, Chiesa R. Analysis of stroke after TEVAR involving the aortic arch. Eur J Vasc Endovasc Surg. 2012;43(3):269–75.
41. Bockler D, Brunkwall J, Taylor PR, Mangialardi N, Husing J, Larzon T, et al. Thoracic Endovascular Aortic Repair of Aortic Arch Pathologies with the Conformable Thoracic Aortic Graft: Early and 2 year Results from a European Multicentre Registry. Eur J Vasc Endovasc Surg. 2016;51(6):791–800.
42. Rohlffs F, Tsilimparis N, Saleptsis V, Diener H, Debus ES, Kolbel T. Air embolism during TEVAR: carbon dioxide flushing decreases the amount of gas released from thoracic stent-grafts during deployment. J Endovasc Ther. 2017;24(1):84–8.
43. Li C, Xu P, Hua Z, Jiao Z, Cao H, Liu S, et al. Early and midterm outcomes of in situ laser fenestration during thoracic endovascular aortic repair for acute and subacute aortic arch diseases and analysis of its complications. J Vasc Surg. 2020;72(5):1524–33.
44. Ahmad W, Buse C, Kroger JR, Mylonas S, Majd P, Brunkwall S, et al. A shorter aortic arch sealing ring (<10 mm) distal to the most distal chimney seems to be an additional important factor contributing to a gutter endoleak in aortic arch TEVAR. Ann Vasc Surg. 2019;61:116–23.
45. Eggebrecht H, Thompson M, Rousseau H, Czerny M, Lonn L, Mehta RH, et al. Retrograde ascending aortic dissection during or after thoracic aortic stent graft placement: insight from the European registry on endovascular aortic repair complications. Circulation. 2009;120(Suppl 11):S276–81.
46. Dong ZH, Fu WG, Wang YQ, Guo DQ, Xu X, Ji Y, et al. Retrograde type A aortic dissection after endovascular stent graft placement for treatment of type B dissection. Circulation. 2009;119(5):735–41.

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Conflict of Interest
None

Authorship
Wael Ahmad: Conceptualization, methodology, data curation, analysis, validation, writing-original draft, review and editing. *Moritz Wegner:* Methodology, data curation, analysis, validation, writing-original draft, review and editing. *Bernhard Dorweiler:* Methodology, analysis, validation, writing-original draft, review and editing.

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ORCID
Wael Ahmad
https://orcid.org/0000-0001-5090-3468

Correspondence address
Priv.-Doz. Dr. Wael Ahmad
Klinik und Poliklinik für Gefäßchirurgie – Vaskuläre und Endovaskuläre Chirurgie
Herzzentrum-Uniklinik Köln
Kerpener Straße 62
50937 Köln
Germany

waelsahmad@gmail.com

Original communication

Cardiovascular risk factors in Sub-Saharan African women

Insights from the TAHES study

Lucie Chastaingt[1,4,5,6], Gwladys N. Gbaguidi[2,4], Julien Magne[3,4,5,6], Pierre-Marie Preux[4,5,6], Victor Aboyans[3,4,5,6], Dismand Houinato[2], and Philippe Lacroix[1,4,5,6] on behalf of TAHES group

[1] Department of Vascular Medecine, Dupuytren 2 University Hospital, Limoges, France
[2] Laboratory of Epidemiology of Chronic and Neurologic Diseases, Faculty of Health Sciences, University of Abomey-Calavi, Cotonou, Benin
[3] Department of Cardiology, Dupuytren 2 University Hospital, Limoges, France
[4] Univ. Limoges, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, Limoges, France
[5] Inserm, U1094, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Limoges, France
[6] IRD, U270, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Limoges, France

Summary: *Background:* Cardiovascular risk factors (CVRF) are associated with major cause of death and disability in Sub-Saharan Africa, especially in women. The contribution of obstetrical, psychological, and socio-economic factors in CVRF are not yet well described in Africa. We aimed to compare the prevalence of CVRF between men and women, and to determine the factors associated to these sex-related differences. *Patients and methods:* A cross-sectional study was conducted on the 2019 data of the TAHES cohort in a geographically defined general population in Benin. A standardized questionnaire adapted from the World Health Organization (WHO) STEPS instrument was used to collect data. Univariate and multivariate analysis has been performed to determine CVRF differences in both sexes. Women-specific logistic regressions have been performed on CVRF previously identified as positively associated to female sex, to assess their association with socio-economic, psychological, and obstetrical factors. *Results:* We included 1583 patients, with a median age of 39 years [range: 32–53 years]. Prevalence of diabetes (1.2% vs. 3.4%, p=0.0042), abnormal kidney function (15.5% vs. 8.4%, p=0.0002), obesity (12.5% vs. 4.1%, p<0.0001), tobacco-smoking (3.4% vs. 14.1%, p<0.0001) and reduced physical activity (69.9% vs. 50.7%, p<0.0001) differed significantly between women and men, respectively. In multivariate analysis, female sex was independently and significantly associated with obesity, anxiety, depression and reduced physical activity. Number of pregnancies was associated with a reduced physical activity. Hypertension was associated with gestational hypertension. *Conclusions:* Obesity and reduced physical activity are significantly and independently more frequent in Beninese women than the male counterparts. Hypertension prevalence in Benin is alarming in both sexes. Targeted prevention strategies against obesity, gestational hypertension and sedentary lifestyle are advocated in African women.

Keywords: Africa, women, cardiovascular, risk factors, sedentary behavior, epidemiology, gestational hypertension

Introduction

An epidemiological transition is ongoing in SubSaharan Africa (SSA), from communicable to non-communicable diseases [1]. Currently, the risk of death secondary to non-communicable diseases is the highest in African countries for both sexes [2]. Non-communicable diseases are rising quickly, and will be the first cause of death in Africa in 2030 [3]. Among them, cardiovascular diseases have a heavy burden [3]. Cardiovascular diseases are influenced by numerous cardiovascular risk factors (CVRF), such as age, obesity, hypertension, dyslipidemia, diabetes, abnormal kidney function [4, 5] as well as psychosocial factors [4, 6].

Women in SSA have the highest death rate due to hypertension in the world [7]. They also have the highest impact of obesity on DALY [7]. Despite all those data, very few studies have been performed to determine cardiovascular risk factors prevalence and their associated factors in this population. Moreover, the link between cardiovascular issues and obstetrical status in this area remains unclear, while the birth rate is high and pregnancy could lead to cardiovascular diseases [8]. Countries in SSA are mostly categorized as low-income countries with poor access to drugs.

Prevention should play an important role in their public health politics to limit the social and economic impact of cardiovascular diseases.

Our primary objective was to describe CVRF prevalence in an SSA community and to compare them between men and women. Our secondary objective was to determine clinical and socio-economic factors associated with CVRF, and their specificities according to sex.

Patients and methods

The TAHES cohort

TAHES is an epidemiological survey started in 2015 and conducted in a rural community of Benin (Tanvé), focused on cardiovascular diseases. The protocol and its feasibility were reported. All patients were recruited by a door-to-door approach, whatever was their health condition. They were invited to undergo a medical examination the day after their inclusion at the local health center. A standardized questionnaire adapted from the World Health Organization (WHO) STEPS instrument was used to collect data [9]. In addition to the standard questionnaire, information on previous pregnancies and creatinine measurement were collected. All data were anonymized. This study was conducted in accordance with General Data Protection Regulation (GDPR) laws and Helsinki's human rights declaration and subject consent required. Our study protocol was declared to the local ethic comity (visa N° 0411/CLERB-UP/P/SP/R/SA).

Study population

A cross-sectional study on the 2019 data of the TAHES cohort was performed. In 2019, obstetrical and renal data have been recorded for the first time. All consecutive patient ≥25 years were included. Younger citizens were not included, considering the very low prevalence of cardiovascular disease below 25 years. Exclusion criterion were a history of severe mental deficiency, a current pregnancy, and living in Tanvé area for less than 6 months.

Socio-economic and demographic data

Socio-economic data were marital status, education level, professional category, frequency of fruits and vegetables intakes, frequency of salt consumption, alcohol intake during the last 30 days, current smoking, and weekly-physical activity. All data were declared by subjects. Demographic data were sex and age.

Clinical data

Clinical data were obstetrical history, anthropometric data, psychological status, blood pressure on both arms, diabetes, and abnormal kidney function.

Obstetrical history

Obstetrical data consisted in the number of pregnancies, age at the first and the last pregnancy and gestational hypertension. Missing data have not been replaced. Late pregnancy was defined as a first and/or a last pregnancy at 35 years old or older.

Anthropometric data

Anthropometric data consisted in weight, height, and Body mass index (BMI). BMI value was determined as: BMI=weight (kg)/height (m)^2.

Psychological status

Psychological status was determined by 9-items Goldberg scale for anxiety and depression. At least 5 symptoms in anxious dimension were necessary to consider the person as anxious. At least 2 symptoms in depressive dimension were necessary to consider the person as depressed.

High blood pressure

ESC recommendations were used to define high blood pressure. Three measures were realized on each arm. The two last measures were averaged for each arm. The highest mean was considered as the person's blood pressure value. Hypertension was defined as a history of hypertension requiring medical treatment or a systolic blood pressure ≥140 mmHg/a diastolic blood pressure ≥90 mmHg during physical examination.

Diabetes

Diabetes was defined as a current intake of antidiabetic drugs or a fasting glycemia equal or above 1.26 g/l. Only one fasting glycemia measurement was performed during data collection.

Abnormal kidney function

Abnormal kidney function was defined as an estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m^2. CKD-Epi formula was used, adjusted on sex, ethnicity and creatinemia value. Creatinemia values from subjects with technical issue were missing and not replaced (n=238).

Statistical analysis

Variable's distribution was defined as not normal by Shapiro-Wilk test. Continuous variables were reported using median (interquartile range) and categorical variables using n (percentage). Qualitative variables were compared using Pearson's χ^2 or Fisher exact test, while Mann-Whitney test was used to compare quantitative variables according to sex. Odds-ratio (OR) with their 95% confidence interval ([95%CI]) and their p-value were determined for each variable according to sex. A p-value ≤0.25 at univariate analysis was required for inclusion in multivariate analysis.

Backward stepwise logistic regressions were performed on CVRF and socio-economic variables in general population, to confirm their significant and independent association with female sex. A second logistic regression was performed focusing on CVRF in female population, to include women-specific factors, such as obstetrical data. OR with 95%CI and p-value were determined (p-value threshold ≤0.05).

All statistical analyses were performed on JMP Pro (version 16.0.0, SAS INSTITUTE JMP, Brie Comte Robert, France), and JASP (version 0.14.0.1, Amsterdam University, Amsterdam, the Netherlands).

Results

General population analysis

Overall, 1 583 subjects (973 women, 61.5%) were included. Population characteristics are displayed in Tables I and II. Diabetes, alcohol consumption and smoking were significantly more prevalent in male population. Women were significantly more frequently obese (12.5%), anxious (11.7%), depressed (22.4%), with abnormal kidney function (15.5%), no education (74.7%) and a limited physical activity (<3 days a week) (69.9%). Age, history of hypertension, salt consumption and fruits/vegetables intake were similar in both sexes. Means of transports in the general population are car (5%), motocycle (61.3%) and bike (22.2%). Men used significantly more bikes and motocycle than women (p<0.001), while no significant difference was found regarding car (p=0.544).

Multivariate analysis results are displayed in Table III. Female sex was significantly and independently associated with obesity (p<0.001) and reduced physical activity (p<0.001), while association to abnormal kidney function had borderline results (p=0.057). Significant association was also found with socio-economic variables, such as anxiety (p<0.001) and having no education (p<0.001).

Cardiovascular risk factors in women

In the female population, median number of pregnancies was 6 [4, 5, 6, 7, 8] and median age at first pregnancy was 20 [17, 18, 19, 20, 21, 22]. We found that 33.3% of women have been concerned by a late pregnancy, and 10.4% by gestational hypertension. In a specific analysis limited to women, we added obstetrical data along with CVRF. Obesity was significantly and independently associated with age (OR 0.972 [0.958–0.985], p<0.001) and hypertension (OR 2.956 [2.042–4.279], p<0.001). Limited physical activity was significantly and independently associated with increased number of pregnancies, monthly amount of alcohol consumption, limited vegetables intake and being a farmer or an independent occupation (Figure 1). Hypertension was significantly and independently associated with age, obesity and gestational hypertension (Figure 2). Regarding LEAD in women population, no specific associated factor has been found.

Discussion

To the best of our knowledge, our study is the first to compare the CVRF in the two sexes in a SSA community. Our study shows differences between men and women regarding cardiovascular risk factors prevalence. Compared to male, female participants had significantly and higher rates of obesity, abnormal kidney function and limited physical activity. Hypertension prevalence was similarly high in both sexes.

Hypertension and obesity prevalence are higher in our population than the 13–14% and 9–27% reported by literature [10, 11, 12]. On the other hand, chronic kidney disease and smoking prevalences are consistent with the 15.8–17% and the 0.4–71% respectively reported [11, 13]. Kerekou et al. noticed a higher limited physical activity prevalence than ours, from 51.8% for men to 62.2% for women [14]. There is an important discrepancy regarding diabetes prevalence, ranging from 0% to 16% elsewhere in SSA [15]. However, our data regarding diabetes are consistent with Price et al. results, who found a 2–3% prevalence in a >30 years old population [10]. Thus, LEAD prevalence is higher than CHD prevalence, which is consistent with previous studies on European and North-American populations [16].

By comparison with European countries, our general population is less concerned by diabetes (2% vs. 11%) [17], obesity (9% vs. 23%) [18] and limited physical activity (10.8% vs. 30%) [19]. However, hypertension prevalence is similar (32% vs. 30–45%) [20]. We can also highlight the low prevalence of smoking in our population, while the worldwide one is established at 22.3% by the World Health Organization [21]. Smoking is still not well considered in SSA countries, which could explain this result.

We found that women had significantly and independently higher rates of obesity and limited physical activity. Obesity was more frequent in younger women and those with hypertension. Regarding the high prevalence of sedentary lifestyle and its association to female sex, specific educational strategies must be implemented to promote physical activity among women, and especially in those with no pregnancies and/or obesity. Public health politics in SSA countries should adjust to the rise of obesity and limited physical activity [22].

Hypertension prevalence was not different according to sex. However, the prevalence was similar to the worldwide one, while previously projected prevalence in Africa was 17.4% in 2025 [12]. This high prevalence is alarming,

Table I. Population characteristics according to sex

Variable	General population (n=1583)	Women (n=973, 61.5%)	Men (n=610, 38.5%)	p-value
Age, median [IQR]	39 [32–53]	39 [32–53]	40 [33–52]	0.2068
Marital status, n (%)				<0.0001
Married/ in a relationship	1321 (83.5%)	764 (78.5%)	557 (91.3%)	
Widower/divorced	219 (13.8%)	199 (20.4%)	20 (3.3%)	
Single	43 (2.7%)	10 (1%)	33 (5.4%)	
Education level, n (%)				<0.0001
No education	1003 (63.4%)	727 (74.7%)	276 (45.2%)	
Occupation, n (%)				<0.0001
Independant	1092 (70%)	738 (75.8%)	354 (58%)	
Farmer	257 (16.2%)	109 (11.2%)	148 (24.3%)	
Employee	94 (5.9%)	45 (4.6%)	49 (8%)	
Inactive	140 (8.8%)	81 (8.3%)	59 (9.7%)	
Fruits consumption, n (%)				
<3 days/week	665 (42%)	413 (42.5%)	252 (41.3%)	0.6562
Vegetables consumption, n (%)				
<3 days/week	171 (10.8%)	96 (9.9%)	75 (12.3%)	0.1298
Salt use in supply, n (%)				
During cooking				0.5041
Never/sometimes	8 (0.5%)	4 (0.4%)	4 (0.7%)	
Often/always	1575 (99.5%)	969 (99.6%)	606 (99.3%)	
During lunch				0.6952
Never/sometimes	1323 (83.6%)	816 (83.9%)	507 (83.1%)	
Often/always	260 (16.4%)	157 (16.1%)	103 (16.9%)	
Psychological status				
Anxious, n (%)	153 (9.7%)	114 (11.7%)	39 (6.4%)	0.0005
Depressed, n (%)	319 (20.1%)	218 (22.4%)	101 (16.6%)	0.0048
Alcohol consumption, n (%)	764 (48.3%)	353 (36.3%)	411 (67.4%)	<0.0001

Table II. Cardiovascular risk factors and cardiovascular disease according to sex

Variable	General population (n=1583)	Women (n=973, 61.5%)	Men (n=610, 38.5%)	p-value
Blood pressure				<0.0001
Systolic blood pressure values, median [IQR]	122 [98–145]	117 [108–134]	123 [114–135]	0.0689
Diastolic blood pressure values, median [IQR]	81 [64–97]	80 [73–89]	81 [74–89]	0.6471
Hypertension, n (%)	509 (32%)	317 (32.6%)	192 (31.5%)	
Kidney function				
eGFR, median [IQR]	85 [49–121]	83 [68–103]	87 [72–107]	0.0025
Abnormal kidney function, n (%)	174 (13%)	133 (15.5%)	41 (8.4%)	0.0002
Smoking, n (%)	119 (7.5%)	33 (3.4%)	86 (14.1%)	<0.0001
BMI				
BMI, median [IQR]	22.4 [16.5–28.3]	22.7 [20.1–26.3]	22.1 [19.6–25.1]	<0.0001
Obesity, n (%)	147 (9%)	122 (12.5%)	25 (4.1%)	<0.0001
Diabetes, n (%)	32 (2%)	12 (1.2%)	20 (3.4%)	0.0042
Reduced physical activity, n (%)	171 (10.8%)	96 (9.9%)	75 (12.3%)	0.1298
Cardiovascular disease, n (%)	14 (0.9%)	8 (0.8%)	6 (1%)	0.7386
Stroke	6 (0.4%)	2 (0.2%)	4 (0.6%)	0.1795
LEAD	7 (0.4%)	5 (0.5%)	2 (0.3%)	0.5904
Coronary heart disease	1 (0.06%)	1 (0.1%)	0	0.9862

Table III. Cardiovascular risk factors and socio-economic characteristics associated to female sex

	Univariate analysis		Multivariate analysis	
Variable	OR [CI95%]	p-value	OR [CI95%]	p-value
Marital status, n (%)				
Married/ in a Relationship	4.526 [2.212–9.261]	<0.001	2.892 [1.225–6.868]	0.015
Widower/divorced	32.835 [14.123–76.341]	<0.001	29.629 [10.814–81.180]	<0.001
Single	–		–	
Education level				
No education	3.576 [2.884–4.435]	<0.001	3.884 [2.974–5.073]	<0.001
Occupation				
Independant	1.519 [1.061–2.173]	0.022	2.086 [1.265–3.439]	0.004
Farmer	0.536 [0.354–0.814]	0.003	0.514 [0.293–0.900]	0.020
Employee	0.669 [0.395–1.132]	0.134		
Inactive	–		–	
Psychological status				
Anxious	1.943 [1.331–2.838]	<0.001	2.158 [1.343–3.469]	0.017
Depressed	1.455 [1.121–1.890]	0.005	1.340 [0.940–1.912]	0.106
Alcohol consumption	0.276 [0.223–0.341]	<0.001	0.261 [0.203–0.337]	<0.001
Hypertension	1.052 [0.847–1.307]	0.647		
Abnormal kidney function	2.006 [1.386–2.902]	<0.001	1.564 [0.987–2.480]	0.057
Smoking	0.214 [0.141–0.324]	<0.001	0.128 [0.071–0.232]	<0.001
Obesity	3.353 [2.153–5.222]	<0.001	6.293 [3.413–11.604]	<0.001
Diabetes	0.363 [0.176–0.748]	0.006	0.255 [0.096–0.676]	0.006
Reduced physical activity	2.261[1.833–2.788]	<0.001	1.830 [1.371–2.44]	<0.001

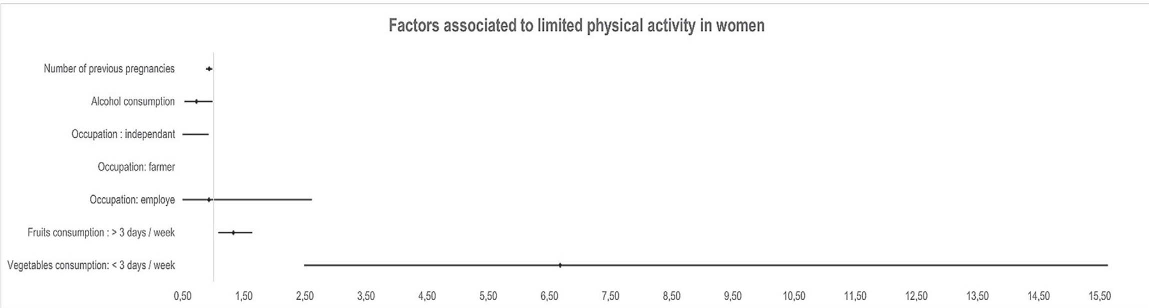

Figure 1. Associated factors to limited physical activity (<3 days/week) in women.

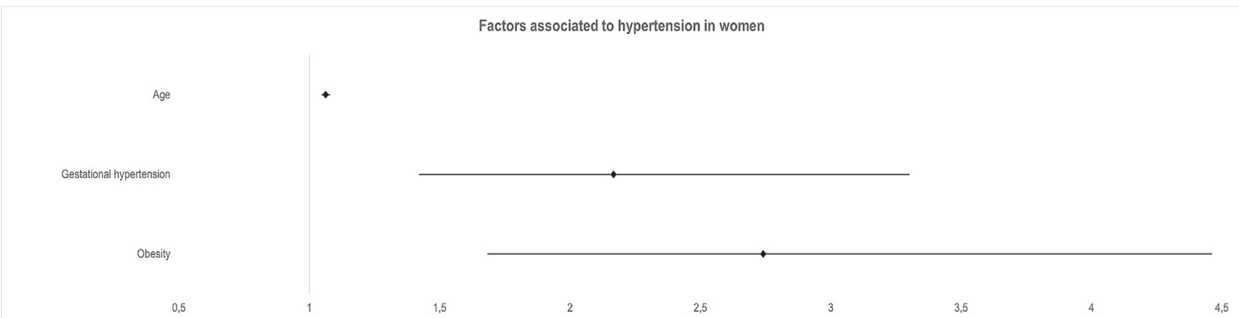

Figure 2. Associated factors to hypertension in women.

considering hypertension as the sixth risk factor in term of attributable global burden disease in western SSA countries [23]. Regarding the high salt-consumption in this area, specific preventive actions are mandatory. In addition to hypertension high prevalence, we can notice that fruit and vegetables intakes are quite low. Some studies tend to show an inverse association between risk of hypertension and fruits and vegetables consumption [24]. This result is consistent with the current recommendation of both American Heart Association and European Society of Cardiology regarding a high-intake of vegetables and fruits in hypertension treatment [25, 26].

We decided to perform a women-only multivariate analysis on hypertension. We showed that it was linked to gestational hypertension, which prevalence is higher in our population than previously reported in European and Northern-American studies [27, 28, 29]. A bias may be induced by the fact that the questionnaire does not distinguish hypertension occurring during pregnancy from chronic hypertension; however, this high prevalence should advocate for a targeted action.

Limitations

Our study was based on a general population and reported original data. However, limitation needs to be acknowledged. First, our population lived in a rural area, limiting extrapolation of the present results to urban areas.

Collected data did not include several variables, such as HIV status, dyslipidemia, familial cardiovascular disease history. Some obstetrical data (history of pre-eclampsia, birth weight of infant, gestational diabetes, prematurity) were also lacking. Although numerous declarative data have been included and are submitted to recall bias, this effect has been limited by using WHO STEP protocol and systematic answers control during inclusion. Finally, study design allowed us to show association between variables, not to define risk factors.

Conclusions

In sub-Saharan Africa, the prevalence of obesity and limited physical activity is high and significantly higher than male counterparts. In addition, the number of pregnancies in Beninese women seem to be associated with CVRF like limited physical activity, while gestational hypertension is associated with hypertension. Longitudinal analysis should be performed to confirm those associations. In the meantime, high prevalence of hypertension, limited physical activity and obesity in a young-age female population should lead to targeted public-health actions, focusing on healthy diet and physical activity.

References

1. thelancet.com [Internet]. Global Burden of Disease 2019. [cited 2021 May 20]. Available from: https://www.thelancet.com/infographics/gbd-2019
2. NCD Countdown 2030 collaborators. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. Lancet. 2018;392(10152):1072–88.
3. World Health Organization. Global status report on noncommunicable diseases 2010 [Internet]. World Health Organization, 2011. Available from: https://apps.who.int/iris/handle/10665/44579
4. World Health Organization [Internet]. Cardiovascular diseases (CVDs). [cited 2021 Jun 2]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
5. Parikh NI, Hwang S-J, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. Arch Intern Med. 2006;166(17):1884–91.
6. Johnson HM. Anxiety and hypertension: is there a link? A literature review of the comorbidity relationship between anxiety and hypertension. Curr Hypertens Rep. 2019;21(9):66.
7. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982–3021.
8. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007; 335(7627):974.
9. Houehanou YC, Mizéhoun-Adissoda C, Amidou S, Désormais I, Houénassi M, Preux P-M, et al. Feasibility of a cardiovascular cohort in a Sub-Saharan Africa community: preliminary report of the pilot project TAHES (Tanvè Health Study) in Benin. Glob Health Action. 2017;10(1):1270528.
10. Price AJ, Crampin AC, Amberbir A, Kayuni-Chihana N, Musicha C, Tafatatha T, et al. Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi. Lancet Diabetes Endocrinol. 2018;6(3): 208–22.
11. Dalal S, Beunza JJ, Volmink J, Adebamowo C, Bajunirwe F, Njelekela M, et al. Non-communicable diseases in sub-Saharan Africa: what we know now. Int J Epidemiol. 2011;40(4): 885–901.
12. Twagirumukiza M, De Bacquer D, Kips JG, de Backer G, Stichele RV, Van Bortel LM. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. J Hypertens. 2011;29(7):1243–52.
13. Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. BMC Nephrol. 2018;19(1):125.
14. Kerekou A, Kouanou AA, Bocovo M, Amoussou-Guenou D, Djrolo F, Houinato D. P8 enquête de prévalence de l'inactivité physique en médecine externe au CNHU/HKM de Cotonou. Diabetes & Metabolism. 2014;40 Suppl 1:A32. https://doi.org/10.1016/S1262-3636(14)72302-X
15. Atun R, Davies JI, Gale EAM, Bärnighausen T, Beran D, Kengne AP, et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. Lancet Diabetes Endocrinol. 2017;5(8):622–67.
16. Bauersachs R, Zeymer U, Brière J-B, Marre C, Bowrin K, Huelsebeck M. Burden of coronary artery disease and peripheral artery disease: a literature review. Cardiovasc Ther. 2019;2019:8295054.
17. diabetesatlas.org [Internet]. IDF Diabetes Atlas 2021. [cited 2022 Oct 24]. Available from: https://diabetesatlas.org/atlas/tenth-edition/
18. World Health Organization [Internet]. New WHO report: Europe can reverse its obesity "epidemic". [cited 2022 Oct 24]. Available from: https://www.who.int/europe/news/item/03-05-2022-new-who-report-europe-can-reverse-its-obesity–epidemic
19. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.
20. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.
21. World Health Organization [Internet]. Tobacco. [cited 2022 Aug 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/tobacco

22. Popkin BM, Adair LS, Ng SW. NOW AND THEN: the global nutrition transition: the pandemic of obesity in developing countries. Nutr Rev. 2012;70(1):3–21.
23. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380 (9859):2224–60.
24. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336(16):1117–24.
25. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e563–95.
26. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018;39(33):3021–104.
27. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39(34):3165–241.
28. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obstet Gynecol. 2000;183(1):S1–22.
29. Savitz DA, Danilack VA, Engel SM, Elston B, Lipkind HS. Descriptive epidemiology of chronic hypertension, gestational hypertension, and preeclampsia in New York State, 1995–2004. Matern Child Health J. 2014;18(4):829–38.

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Conflict of Interest

VA declares following conflicts of interest unrelated to this study: Bayer, BMS, Boehringer-Ingelheim, NovoNordisk. LC, GNG, JM, PMP, DH and PL declare none.

Correspondence address
Lucie Chastaingt, MD
Department of Vascular Medecine & Vascular Surgery
DUPUYTREN 2 University Hospital
16 rue Bernard Descottes
87042 Limoges
France

lucie.chastaingt@chu-limoges.fr

Original communication

An angiosome-centred approach for TcpO2 electrode positioning

A pilot study

Judith Catella[1,2,4], Nellie Della Schiava[5,6], Fortunat L'Hoia[1], Patrick Lermusiaux[5,6], Antoine Millon[5,7], and Anne Long[1]

[1] Service de Médecine Interne et Vasculaire, Hôpital Edouard Herriot, Hospices Civils de Lyon, France
[2] Laboratoire d'Excellence du Globule Rouge (Labex GR-Ex), Sorbonne, Paris, France
[3] Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM) EA7424, Université Claude Bernard Lyon 1, Université de Lyon, France
[4] UMR 5305: Laboratoire de Biologie Tissulaire et Ingénierie Thérapeutique, Institut de Biologie et Chimie des Protéines, CNRS/Université Claude Bernard Lyon 1, France
[5] Service de Chirurgie Vasculaire et Endovasculaire, Groupement Hospitalier Est, Hôpital Louis Pradel, Hospices Civils de Lyon, Bron, France
[6] Institut National des Sciences Appliquées Lyon, Laboratoire de Génie Electrique et Ferroélecricité EA 682, Villeurbanne, France
[7] Laboratoire CarMeN, INSERM U1060, Université Claude Bernard Lyon 1, Bron, France

Summary: *Background:* The latest guidelines propose a TcpO2 value of 30 mmHg to help to confirm the diagnosis of chronic limb threatening ischemia. However, placement of electrodes is not standardised. The relevance of an "angiosome-centred" approach for TcpO2 electrode positioning has never been evaluated. We therefore retrospectively analysed our TcpO2 results to study the impact of electrode placement on the different angiosomes of the foot. *Patients and methods:* Patients consulting the vascular medicine department laboratory for suspicion of CLTI using TcpO2 electrodes placement on the different angiosome arteries of the foot (first inter metatarsal space, lateral edge of the foot and plantar side of the foot) were included. As the mean intra-individual variation is reported to be 8 mmHg, a variation of mean TcpO2 for the 3 locations ≤8 mmHg was considered to be not clinically significant. *Results:* Thirty-four patients (34 ischemic legs) were analysed. The mean TcpO2 was higher at the lateral edge of the foot (55 mmHg) and plantar side of the foot (65 mmHg) than at the first intermetatarsal space (48 mmHg). There was no clinically significant variation of mean TcpO2 according to anterior/posterior tibial artery patency and fibular artery patency. This was present when stratifying on the number of patent arteries. *Conclusions:* The present study suggests that multi-electrode TcpO2 is not useful to assess tissue oxygenation in the different angiosomes of the foot to guide surgical decision; first intermetatarsal electrode alone would be preferred. TcpO2 seems rather to evaluate overall tissue oxygenation of the foot. Electrode location on the plantar side of the foot may overestimate results and lead to misinterpretation.

Keywords: Chronic limb threatening ischemia, TcpO2, angiosome, peripheral arterial disease

Introduction

Atherosclerotic disease is the primary cause of lower extremity arterial disease (LEAD) [1]. LEAD affects more than 200 million people worldwide and is a common cause of vascular morbidity [2]. Chronic limb-threatening ischaemia (CLTI) is the terminal stage of LEAD; CLTI is characterised by intractable foot pain at rest, wounds, tissue ulcers and/or necrosis, present for at least 2 weeks. Patients with CLTI represent approximately 2–3% of all LEAD [3].

Transcutaneous oximetry (TcpO2) measures oxygen diffusion at the skin surface using electrodes, and the latest guidelines propose a TcpO2 value of 30 mmHg to help to confirm the diagnosis of CLTI or predict wound healing [4, 5]. However, in a systematic review Leenstra et al. reported that placement of electrodes was not standardised as in a fifth of studies (n=7, 19%) were simply "adjacent" to an ischaemic lesion, and, although in two-thirds of studies (n=24, 67%) electrodes were on specific anatomical locations (dorsum of the foot for the majority) [6], placement was not based on the angiosome principle first described in 1987 [7]. This concept is based on anatomical studies, and delineates the human body into three-dimensional tissue blocks irrigated by specific arteriovenous sources. In the foot 5 angiosomes have been described, arising from the posterior tibial artery (n=3; including those that arise from the lateral and medial plantar arteries), the anterior tibial artery (n=1), and the peroneal artery (n=1; Figure 1). Applied to the lower limb, it may help the surgeon to decide a specific strategy for revascularisation [8].

The relevance of an "angiosome-centred" approach for TcpO2 electrode positioning has never been evaluated.

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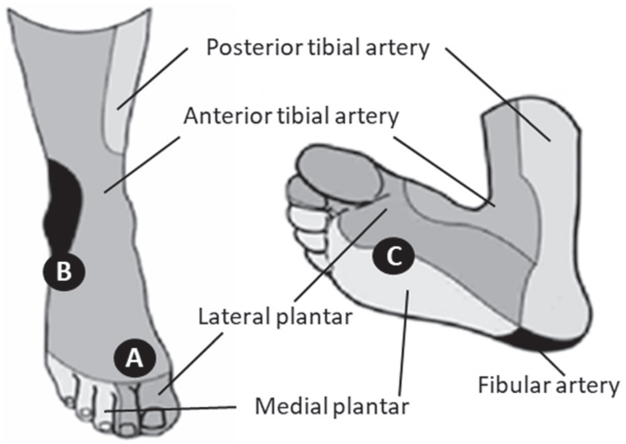

Figure 1. Foot Angiosome model; Electrode placement. A: First intermétatarsal space; B: Lateral edge of the foot; C: Plantar face.

We therefore retrospectively analysed our TcpO2 results to study the impact of electrode placement on the different angiosomes of the foot.

Patients and methods

Data source

Medical records of all patients assessed for suspicion of CLTI by TcpO2 measurement in the Vascular Medicine Department Laboratory of the Edouard Herriot hospital, Lyon, France (part of the university hospitals of Lyon, Hospices Civils de Lyon) from November 2020 to March 2021 were retrospectively identified. The protocol was approved by the Institutional Review Board of the Hospices Civils de Lyon (number 21_5418).

Patient selection criteria

Patients were included if they consulted in the clinic for suspicion of CLTI using TcpO2 electrodes placement on the different angiosomes of the foot. We considered three locations. One electrode was on the first intermetatarsal space covering the anterior tibial artery angiosome. A second electrode was on the lateral edge of the foot for the fibular artery angiosome. A third electrode was on the plantar side of the foot, on the true plantar surface, covering the posterior tibial artery angiosome (Figure 1).

Patients were excluded if under 18 years of age, if the follow-up was outside of the Hospices Civils de Lyon or if no data about arterial patency was available (when patients were referred to our hospital only for TcpO2 testing); those with ilio-femoro-popliteal obstructive disease were not excluded.

Study variables

Data collected were patient baseline characteristics including aetiology of CLTI, cardiovascular risk factors, cardiovascular comorbidities, cardiovascular medications, and location of the wound, as was the TcpO2 value for each location was collected. We also collected patency of fibular, posterior, and anterior tibial arteries. Arteries were considered patent in case of permeability irrespective of the degree of stenosis. Patency was documented according to available imaging, considering preferentially the results of arteriography first, then those of computed tomography, and finally Doppler-ultrasonography. During follow-up, the collected outcomes were osteitis, revascularization, amputation and death.

Measurements

Ankle pressure and toe systolic pressure were measured according to standard operating protocols. TcpO2 measurements were performed using TCM 400 Monitor (Radiometer®, Neuilly-Plaisance, France) set to default temperature at 43 degrees Celsius. Patients were in the supine position and asked to not speak during measurement. TcpO2 values were collected after 20 minutes of recording and after stabilisation. A value was considered of good quality if the measurement showed an initial fall. Patients were asked, as far as possible, not to smoke or drink coffee/tea in the two hours before measurement to avoid vasoconstriction. A TcpO2 $\geq$95 mmHg was considered as an outlier value.

Data analysis

The primary endpoint was the mean TcpO2 value according to artery patency in each angiosome. The secondary endpoint was the mean TcpO2 value according to the number of patent arteries. Descriptive variables are reported as means±standard deviation (SD). Because the mean intra-individual variation is reported to be 8 mmHg, we considered that a variation of mean TcpO2 for the 3 locations $\leq$8 mmHg was not clinically significant [9].

Results

Thirty-four patients (34 ischemic legs) were analysed. The majority of patients were male, the mean age was 72.7 years, and the mean body mass index was 27.5 kg/m^2. Diabetes mellitus was the most frequent cardiovascular risk factor (73.5%; Table I). Wound location was: toes for 19 (55.9%) patients, heel for 7 (20.6%) patients, transmetatarsal amputation scar for 2 (5.9%) patients, leg for 5 (14.7%) patients, and foot without detail for 2 patients. Nine (26.5%) patients presented with osteitis.

Ankle systolic pressure was measured in 10 (29.4%) patients; the mean±SD ankle systolic pressures were 103 ±32 mmHg in the anterior tibial artery and 75±52 mmHg in the posterior tibial artery, corresponding to a mean±SD ankle brachial index of 0.76±0.19 and 0.66±0.20, respectively. The systolic toe pressure was measured in 8 (23.5%) patients; the mean±SD systolic toe pressure

Table I. Clinical characteristics of the patients

	Total population, n=34
Sex, male, n (%)	24 (70.6)
Mean age, years (SD)	72.7±15.7
Mean body weight, kg (SD)	76.3±15.5
Mean height, cm (SD)	167±11
Mean body mass index, kg/m^2 (SD)	27.5±5.8
Previous cardiovascular history, n (%)	
Former or current smoker	17 (50.0)
Diabetes mellitus	25 (73.5)
Hypertension	23 (67.6)
Hypercholesterolemia	12 (35.3)
Severe renal impairment or transplant	11 (32.4)
Stroke/TIA	10 (29.4)
Coronaropathy	18 (52.9)
Atrial fibrillation	16 (47.1)
Ongoing treatment, n (%)	
Antiplatet agent	26 (76.5)
Anticoagulants	14 (41.2)
Statin	26 (76.5)
ACE inhibitors/ARB, n (%)	19 (55.9)

Notes. SD: standard deviation; ACE: angiotensin converting enzyme; ARB: angiotension receptor blockers.

was 63±18 mmHg corresponding to a mean±SD toe brachial index of 0.41±0.12.

Infragenicular arteries patency characteristics are described in Table II. Artery patency was documented by arteriography in 12 (35.3%) legs, by computed tomography in 9 (26.5%) legs, and by Doppler ultrasonography in 13 (38.2%) legs. Seven (20.6%) legs had no patent artery and 8 (23.5%) had three patent arteries. The proportion of legs with posterior tibial artery patency was 50.0% (n=17), with anterior tibial artery patency was 47.1% (n=16), and with anterior tibial artery was 58.8% (n=20; Table II).

Table II. Infragenicular arteries patency

	Total legs, n=34
Documentation, n (%)	
Arteriography	12 (35.3)
Computed tomography	9 (26.5)
Doppler-ultrasonography	13 (38.2)
Patency, n (%)	
Legs without patent artery	7 (20.6)
Legs with 1 patent artery	9 (26.5)
Legs with 2 patent arteries	10 (29.4)
Legs with 3 patent arteries	8 (23.5)
Posterior tibial artery patency	17 (50.0)
Anterior tibial artery patency	16 (47.1)
Fibular artery patency	20 (58.8)

TcpO2 measurements

Considering measurement at the first intermetatarsal space, one (2.9%) measurement was inconclusive/impossible. A total of 6 (17.6%) measurements at the lateral edge of the foot, and 8 (23.5%) measurements at the plantar side of the foot were either inconclusive or impossible (Table III).

Table III. TcpO2 value according to artery patency

	Total legs, n=34
First intermetatarsal space	
Inconclusive, n (%)	1 (2.9)
Mean TcpO2 for all legs, mmHg±SD	48±21
Mean TcpO2 for legs with patent anterior tibial artery, mmHg±SD	52±23
Mean TcpO2 for legs with occluded anterior tibial artery, mmHg±SD	44±18
Mean TcpO2 for legs with 0–1 patent artery, mmHg±SD	40±20
Mean TcpO2 for legs with 2–3 patent arteries, mmHg±SD	54±19
Lateral edge	
Inconclusive, n (%)	6 (17.6)
Mean TcpO2 for all legs, mmHg±SD	55±16
Mean TcpO2 for legs with patent fibular artery, mmHg±SD	57±12
Mean TcpO2 for legs with occluded fibular artery, mmHg±SD	53±12
Mean TcpO2 for legs with 0–1 patent artery, mmHg±SD	49±11
Mean TcpO2 for legs with 2–3 patent arteries, mmHg±SD	60±13
Plantar side of the foot	
Inconclusive/impossible, n (%)	8 (23.5)
Mean TcpO2 for all legs, mmHg±SD	65±23
Mean TcpO2 for legs with patent posterior tibial artery, mmHg±SD	71±22
Mean TcpO2 for legs with occluded posterior tibial artery, mmHg±SD	58±24
Mean TcpO2 for legs with 0–1 patent artery, mmHg±SD	55±22
Mean TcpO2 for legs with 2–3 patent arteries, mmHg±SD	72±21

Notes. SD: standard deviation.

Table IV. Intermetarsal fist space TcpO2 value in the legs according to surgical decision

	Total legs, n=34
Revascularised legs, n (%)	15 (44.1)
Yes: mean TcpO2, mmHg±SD	39±22
No: mean TcpO2, mmHg±SD	56±15
Amputated legs, n (%)	11 (32.4)
Yes: mean TcpO2, mmHg±SD	39±21
No: mean TcpO2, mmHg±SD	52±19
Hyperbaric oxygen therapy, n (%)	5 (14.7)
Yes: mean TcpO2, mmHg±SD	55±19
No: mean TcpO2, mmHg±SD	45±21

Notes. SD: standard deviation.

We observed a steady decrease in some legs for plantar side of the foot measurement instead of an initial fall. Six patients (17.6%) were unable to position themselves so as the electrode plantar side of the foot could be placed and 2 electrodes were unstick (5.9%); the mean±SD age of these patients was 84.5±7.1 years. There were also 3 patients with an outlier plantar side TcpO2 value; the mean±SD age of these patients was 77.7±14.2 years while this was 70.4±17.0 years for other patients.

The mean TcpO2 was higher at the lateral edge of the foot (55 mmHg) and plantar side of the foot (65 mmHg) than at the first intermetatarsal space (48 mmHg). There was no clinically significant variation of mean TcpO2 according to anterior and posterior tibial artery patency and fibular artery patency; this was present when stratifying on the number of patent arteries (Table III).

Surgical decision

A revascularization was decided for 15 (44.1%) legs; the mean first intermetatarsal space TcpO2 in revascularised legs was 39 mmHg. An amputation was decided for 11 (32.4%) legs, 3 of which had osteitis; the mean first intermetatarsal space TcpO2 in amputated legs was 39 mmHg. Five (14.7%) patients had hyperbaric oxygen therapy (Table IV).

Discussion

To date, there is no consensus on TcpO2 electrode placement to diagnose suspected CLTI, and the angiosome is an interesting concept based on three dimensional division of the foot to guide surgeons' choice of revascularization in case of ulcers (8). In this retrospective study, we analysed the value of placing electrodes on each angiosome artery of the foot and the results suggest that placing one electrode in each of the 3 foot angiosome arteries is not superior to a single electrode in the usual first intermetatarsal space.

Electrode placement on the plantar side of the foot is very uncommon [10]. Patients have to position themselves in a particular way to install both the contact liquid and the electrode without any air bubble and to obtain good impermeability of the measuring site. This is difficult to obtain in elderly patients with painful extremities, as illustrated by the age of those for whom this impossible, but also the even greater age of those with outlier values. It is also of note that, recently, Udovichenko et al. measured TcpO2 level after electrode placement on the plantar side of the foot, and, as herein, observed a steady decrease instead of the formation of a plateau; the authors also found that the mean TcpO2 value in the medial plantar region was significantly higher than on the back of the foot [11]. A measurement error cannot be ruled out, in particular as the most frequently patent artery was the fibular artery and not the posterior tibial artery. In addition, on the plantar side of the foot, we found a mean value of 65 mmHg, which is high considering that normal TcpO2 is around 60 mmHg, while almost half of them had 2 or 3 infragenicular arteries occluded. Taken together, this suggests that measurement on the site may lead to overestimation of TcpO2 value and to inappropriate therapeutic decision.

As the mean intra-individual variation of TcpO2 is reported to be 8 mmHg [9], a variation of the mean TcpO2 below 8 mmHg cannot be considered as clinically significant. In the present study there was no clinically significant variation of TcpO2 according anterior tibial artery or fibular artery patency. This was, however, observed according to the number of infragenicular patent arteries. TcpO2 value is therefore probably a better reflection of overall tissue oxygenation of the foot than that of a specific angiosome.

Limitations

The present study has some limitations. Firstly, this is a retrospective analysis of a small cohort of 34 patients. Only a third of patients had the gold standard imaging by angiography; Doppler ultrasonography may lack performance to document patency of infrapopliteal arteries. Nevertheless, to the best of our knowledge, it is the first publication of a consecutive series of patients using the angiosome concept. The patients frequently suffered from diabetes, however, it is reported that the TcpO2 measurements were similar in patients with and without diabetes [12]. Furthermore, while there are 5 angiosomes that emerge from the three infragenicular arteries, we used only 3 electrodes. We considered that placing an electrode on the plantar side of the foot was a good compromise to study the 3 different angiosome perfused by posterior tibial artery. Another point is that the mean TcpO2 value found herein is very high for a population of patients with suspected CLTI. However, they were unselected consecutive patients referred to our unity reflecting daily practice. Finally, it was not possible to investigate the potential contribution of ankle pressure and toe blood pressure for the diagnosis of CLTI as many measurements were missing due to wound on the legs or toes, amputated toes, or uninterpretable due to mediacalcosis [13]. A prospective cohort is necessary to confirm these results using arteriography as the gold standard imaging technique and including only patients with infrapopliteal occlusive disease.

Conclusions

The preliminary results of the present study suggest that multi-electrode TcpO2 is not useful to assess tissue oxygenation in the different angiosomes of the foot to guide surgical decision; first intermetatarsal electrode alone would be prefered. TcpO2 seems rather to evaluate overall tissue oxygenation of the foot. Electrode location on the plantar side of the foot may overestimate results and lead to misinterpretation.

References

1. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. Lancet. 2013;382(9901):1329–40.
2. Beckman JA, Creager MA. Critical limb ischemia and intermediate-term survival. JACC Cardiovasc Interv. 2014;7(12): 1450–2.
3. Shishehbor MH, Bunte MC. Time to redefine critical limb ischemia. JACC Cardiovasc Interv. 2017;10(22):2317–9.
4. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763–816.
5. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. 2019;69(6): 3S–125S.e40.
6. Leenstra B, Wijnand J, Verhoeven B, Koning O, Teraa M, Verhaar MC, et al. Applicability of transcutaneous oxygen tension measurement in the assessment of chronic limb-threatening ischemia. Angiology. 2020;71(3):208–16.
7. Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg. 1987;40(2):113–41.
8. Alexandrescu V, Hubermont G. Primary infragenicular angioplasty for diabetic neuroischemic foot ulcers following the angiosome distribution: a new paradigm for the vascular interventionist? Diabetes Metab Syndr Obes. 2011;327.
9. Olerud J, Pecoraro R, Burgess E, McKnight B, Wyss C, Reiber G, et al. Reliability of transcutaneous oxygen tension (TcPO2) measurements in elderly normal subjects. Scand J Clin Lab Invest. 1987;47(6):535–41.
10. Catella J, della schiava N, Calanca L, Steinmetz E, Millon A, Mahé G, et al. Real-world practices of TcPO2 measurements: A French national survey. Vasc Med. 2022;27(4):377–9.
11. Udovichenko OV, Afana'seva DM, Shirshov ON, Dadova LV, Nosenko EM, Berseneva EA, et al. Phenomenon of unstable TcpO2 level in transcutaneous oximetry in patients with diabetes mellitus. Angiol Sosud Khir. 2020;26(1):16–21.
12. Quigley FG, Faris IB. Transcutaneous oxygen tension measurements in the assessment of limb ischaemia. Clin Physiol. 1991;11(4):315–20.
13. Lanzer P, Boehm M, Sorribas V, Thiriet M, Janzen J, Zeller T, et al. Medial vascular calcification revisited: Review and perspectives. Eur Heart J. 2014;35(23):1515–25.

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ORCID
Judith Catella
https://orcid.org/0000-0001-8028-6827
Nellie Della Schiava
https://orcid.org/0000-0002-0374-5994

Correspondence address
Dr Judith Catella
Hospices Civils de Lyon
5 place d'Arsonval
69003 Lyon
France

judith.catella@chu-lyon.fr

Original communication

High prevalence of peripheral and carotid artery disease in patients with interstitial lung diseases

Max Jonathan Stumpf[1,a], Max Fabian Fleddermann[1,a], Marina Michaela Luise Wirtz[1], Leonie Biener[1], Leonie Weinhold[2], Nadjib Schahab[1], Marcel Weber[1], Georg Nickenig[1], Dirk Skowasch[1], Christian Alexander Schaefer[1,a], and Carmen Pizarro[1,a]

[1] Department of Internal Medicine II, Cardiology, Pneumology, and Angiology, University Hospital Bonn, Germany
[2] Institute for Medical Biometry, Computer Science, and Epidemiology, University of Bonn, Germany
[a] These authors contributed equally.

Summary: *Background:* Interstitial lung diseases (ILD) are a heterogenous group of diseases, which have pulmonary fibrosis, restrictive lung disease, and decreased diffusion capacity as a common final path. Premature death frequently results not from ILD itself but from comorbidities. Peripheral artery disease (PAD) is a common comorbid disease in different chronic lung diseases. The focus of the present study is to clarify the prevalence of PAD in ILD. *Patients and methods:* A total of 97 patients with ILD and 30 controls were included in the study. Patients with ILD were subdivided into two groups according to the progression of pulmonary fibrosis: progressive fibrosing and non-progressive fibrosing ILD (PF-ILD and nPF-ILD, respectively). All participants underwent standard angiological and pneumological diagnostic procedures including six-minute walking test, measurement of ankle-brachial-index, and colour-coded duplex sonography. *Results:* We observed no relevant differences in the baseline characteristics except age. Both, PF-ILD and nPF-ILD patients, presented with a highly increased incidence of atherosclerotic lesions compared to the control group ($p<0.001$). PAD was present in all patients with PF-ILD and in 73% of patients with nPF-ILD. These results were confirmed by age-adjusted regression analyses. *Conclusions:* The present results indicate that ILD is an independent risk factor for atherosclerosis. Patients with PF-ILD are more severely affected than nPF-ILD patients with age as a confounding variable. Atherogenesis in ILD may be mediated by increased cardiovascular risk, systemic inflammation and chronic hypoxemia.

Keywords: Interstitial lung disease, idiopathic pulmonary fibrosis, peripheral artery disease, atherosclerosis, IL-6, hypoxia, hypoxia-inducible factor

Introduction

Interstitial lung diseases (ILD) are a highly heterogenous group of diseases encompassing more than 200 different entities [1]. Due to this variety, information on prevalence and incidence of ILD is still vague. The prevalence is estimated to be between 6.3 and 97.9 per 100,000 persons in Europe [2, 3]. Most common entities of ILD are idiopathic pulmonary fibrosis (IPF), stage IV sarcoidosis, and ILD that is associated with connective tissue diseases (CTD-ILD) such as systemic sclerosis or rheumatoid arthritis. Although the diseases that lead to ILD are mostly rare and have their own individual classification and course, they share a common final path leading to pulmonary fibrosis. This is accompanied by restrictive lung disease and decreased diffusion capacity as well as reduced quality of life and premature death [4]. However, frequently not ILD itself but its comorbidities increase the mortality rate [5].

Comorbidities in ILD and IPF, in particular, have been the subject of several research articles, reviews, and register analyses during the last decade [6]. In particular, coronary artery disease (CAD) and myocardial infarction have proven to be independently associated with ILD [7]. Accordingly, patients with IPF suffer from an increased risk of developing myocardial infarction and ischaemic heart disease. Peripheral arterial disease (PAD) is another entity of atherosclerosis and, surprisingly, is estimated to have a much lower prevalence, between 3.6 and 20.0%, amongst patients with ILD [6, 8, 9]. However, most of the underlying studies are limited either by their retrospective design or, in case of register analyses, their dependence on international classification of the diseases (ICD) -codes. This is crucial, as the ICD-codes for CAD or PAD depend on clinical scores such as Fontaine's classification describing walking distance until the occurrence of intermittent claudication. These clinical signs, however, may be absent or masked in patients with ILD, because they often are limited by persistent and severe dyspnoea.

In other lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea (OSA) and advanced stages of sarcoidosis, an increased risk of comorbid atherosclerosis or preatherosclerotic changes have been observed. Here, it is likely that this increased risk is caused by systemic inflammation and/or intermittent hypoxia [10, 11].

Therefore, prevalence of cardiovascular diseases and particularly PAD in ILD has likely been underestimated. Subsequently, the main intention of this study was to prospectively investigate the prevalence of atherosclerosis in patients with ILD. Furthermore, this study aimed to evaluate whether or not progressive-fibrosing ILD is a risk factor for PAD.

Patients and methods

This prospective observational study was conducted according to the principles of the Declaration of Helsinki for Human Research and has been approved by the local ethics committee of the University Hospital in Bonn (application number: 006/19). Written informed consent of all participants was obtained prior to examination.

Patients and controls

From January 2019 to December 2020, a total of 104 consecutive patients diagnosed with ILD were enrolled in the study. Seven patients were excluded because they declined (or were unable) to undergo angiological examinations. Based on the results of lung-function testing, the patients were divided into two groups: progressive-fibrosing ILD (PF-ILD, n=49) and non-progressive fibrosing ILD (nPF-ILD, n=48). PF-ILD was defined according to the INBUILD-criteria [12]: a relative decline in forced vital capacity (FVC) of ≥10% of the predicted value, a relative decline in FVC of 5% to less than 10% of the predicted value accompanied by worsening of respiratory symptoms or progression of pulmonary fibrosis as assessed via high-resolution computed tomography (HR-CT) accompanied by worsening of respiratory symptoms over the course of two years [4, 12]. Patients with ILD who did not match PF-ILD criteria were assigned to the nPF-ILD group. Thirty patients without known pulmonary or vascular disease were recruited as controls.

Pneumological assessment

All patients and controls underwent bodyplethysmography (Bodyplethysmograph JAEGER), to test the diffusion capacity in single breath mode (Alveo-Diffusionstest Jaeger) and a six-minute walk test with blood gas analysis before and after. All parameters were assessed as a standard value and percentage of the predicted value. The latter were calculated by on-board software using reference values provided by the Global Lung Initiative [13]. The corresponding abbreviations are labelled with "%". The following parameters were derived from body plethysmography for further analysis: total lung capacity (TLC, TLC%), forced vital capacity (FVC, FVC%), forced expiratory volume (FEV1, FEV1%), Tiffeneau index (FEV1/FVC), carbon monoxide (CO) diffusion capacity (DLCO%) and CO diffusion coefficient (KCO%). A Six-minute walk test (6MWT) was performed and the following parameters were assessed: distance, oxygen and carbon monoxide partial pressure (pO_2, pCO_2) before and after walking, and Borg-dyspnoea score to determine subjective feeling of dyspnoea [14].

Blood testing

Blood tests were performed including blood count, triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), lipoprotein a, C-reactive protein (CRP), interleukin-6 (IL-6) and HBA_{1C}. These parameters have been proven to accelerate atherogenesis and arterial stiffness [15].

Angiological assessment

Standard angiological diagnostics

All patients and controls underwent standard angiological diagnostic procedures. This included measurement of ankle-brachial-index (ABI) using a Vasolab 320 (ELCAT) and colour-coded duplex sonography (CCDS) performed with a PHILIPS EPIQ 7 ultrasonic platform equipped with a L12-3 linear array scanner. CCDS was applied on lower-limb arteries and cervical arteries. The presence of any atherosclerotic plaque was documented in B-mode and CCDS and resulted in the diagnosis of PAD. Plaque of the cervical arteries was defined by the meeting of two out of three criteria: 1) intima-media thickness >1.5 mm; 2) protrusion into the lumen; 3) abnormal wall texture [16]. Plaque of the lower extremity arteries was defined as abnormal protrusion into the lumen and/or abnormal wall texture. Depending on the affected vascular territory, presence of PAD was subdivided into PAD of lower-limb (peripheral) arteries (pPAD) and PAD of cervical arteries (cPAD). Clinically, participants were subclassified via the Fontaine classification of PAD [17] (Electronic supplementary material [ESM] 1). The onset of claudication was assessed during 6MWT.

Statistical analysis

All variables are described as the mean value±standard deviation or as numbers with percentages, as appropriate. Differences between the baseline characteristics of the groups were calculated via Pearson's Chi-Square and

Table I. Baseline characteristics

	PF-ILD (n=49)	nPF-ILD (n=48)	p^a	Control (n=30)	p^b
Gender (female) [n (%)]	17 (34.7)	21 (43.8)	n.s.	17 (56.7)	n.s.
Age [years]	68.90±10.85	59.04±14.28	<0.001	60.60±11.49	<0.001
Packyears [years]	17.08±20.76	10.95±19.23	n.s.	13.70±24.55	n.s.
Hypertension [n (%)]	22 (44.9)	20 (41.7)	n.s.	12 (40.0)	n.s.
Hypercholesterolemia [n (%)]	21 (43.8)	19 (38.8)	n.s.	6 (20.0)	n.s.
Diabetes [n (%)]	13 (26.5)	10 (20.8)	n.s.	2 (6.7)	n.s.
COPD [n (%)]	7 (14.3)	1 (2.1)	<0.05	0 (0)	<0.05
Asthma [n (%)]	6 (12.2)	8 (16.7)	n.s.	1 (3.3)	n.s.
Time since diagnosis [months]	26.5±53.3	70.2±60.2	<0.001		
ILD subgroups			<0.001		<0.001
IPF [n (%)]	25 (51.0)	0 (0)	/	0 (0)	/
Stage-IV Sacoidosis [n (%)]	2 (4.1)	15 (31.3)	/	0 (0)	/
Rheumatic disease [n (%)]	9 (18.4)	14 (29.2)	/	0 (0)	/
Inhalative toxins [n (%)]	2 (4.1)	2 (4.2)	/	0 (0)	/
CPFE [n (%)]	2 (4.1)	4 (8.3)	/	0 (0)	/
HSA [n (%)]	1 (2.0)	1 (2.1)	/	0 (0)	/
COP [n (%)]	2 (4.1)	2 (4.2)	/	0 (0)	/
Other [n (%)]	6 (12.2)	10 (20.8)	/	0 (0)	/

Notes. [a]PF-ILD vs. nPF-ILD; [b]overall intergroup difference. PF-ILD: progressive-fibrosing interstitial lung disease; nPF-ILD: non-progressive-fibrosing interstitial lung disease; ILD: interstitial lung disease; IPF: interstitial pulmonary fibrosis; CPFE: combined pulmonary fibrosis and emphysema; HAS: hypersensitivity alveolitis; COP: cryptogenic organizing pneumonia; BMI: body mass index; COPD: chronic obstructive pulmonary disease.

Cramer's V test for categorical variables and analysis of variance (ANOVA) for continuous variables.

Additionally, the PF-ILD, nPF-ILD and control groups were compared with regard to PAD and its subclasses, pPAD and cPAD, and Fontaine's classification. Binary outcome variables (PAD, pPAD, cPAD) were analysed via logistic regression models. For the Fontaine classification, ordinal regression analysis was performed. Since only six patients were classified on Fontaine stages IIb and III, classification was simplified to Fontaine stages 0, I, and ≥II for regression analysis. The latter thereby encompassed Fontaine stages IIa, IIb, III and IV. Results are presented as odds ratios (OR) with confidence intervals (CI) for logistic and ordinal regression models. Regression models were adjusted for age, since age differed significantly between the three groups and is an independent predictor of atherosclerosis.

As four outcome variables were examined p-values <0.01 were considered significant (according to Bonferroni correction for multiple testing).

Statistical analyses were conducted using IBM® SPSS® Statistics (version 26) and R (version 4.0.3).

Results

Baseline characteristics, medication, and blood testing

Baseline characteristics

Baseline characteristics are presented in Table I. With a mean age of 68.9±10.9 years, patients with PF-ILD were significantly older compared to controls (60.6±11.5 years; p<0.001) and nPF-ILD patients (59.0±14.3 years; p<0.001). Significantly more patients with PF-ILD (14.3%) also suffered from chronic obstructive pulmonary disease (COPD) in comparison to nPF-ILD patients (2.1%; p<0.05) and controls (0%; p<0.05). No further significant differences were found between the groups, including relevant risk factors for atherogenesis, such as number of packyears, body mass index (BMI), arterial hypertension, hypercholesterolemia, or diabetes.

Medication

Information about the medications taken by the study participants is presented in ESM 2. Administration of oral anticoagulants, encompassing vitamin-K-antagonists and new oral anticoagulants was significantly more frequent in patients with PF-ILD compared to control (p<0.01) and nPF-ILD (p<0.05) patients. Statins (p<0.001), diuretics (p<0.01), long-acting-beta-agonists (LABA, p<0.01) and oral corticosteroids (p<0.001) were found to be more frequent in patients with ILD compared to controls; yet there was no significant difference between PF-ILD and nPF-ILD patients. Notably, two controls reported the intake of LAMA and/or LABA. Of those, one patient was diagnosed with mild allergic asthma, the other reported unspecific dyspnoea, without any signs of COPD or asthma. Both took their medication as needed.

Blood testing

Blood tests revealed largely normal cell counts apart from leucocytes, which were elevated in patients with PF-ILD (9.36±3.13 G/l) and nPF-ILD (8.42±2.80 G/l) compared to the control group (5.36±0.35 G/l; p<0.001). As for risk factors of atherosclerosis, total cholesterol was lower in

Table II. Angiological examination

	PF-ILD (n=49)	nPF-ILD (n=48)	p^a	Control (n=30)	p^b
Mean ABI	1.06±0.21	1.10±0.20	n.s.	1.13±0.89	n.s.
ABI<0.90 [n (%)]	15 (30.6%)	12 (25.0%)	n.s.	2 (6.7%)	<0.05
ABI>1.40 [n (%)]	5 (10.2%)	7 (14.6%)	n.s.	1 (3.3%)	n.s.
Prevalence of PAD [n (%)]	49 (100%)	35 (72.9%)	<0.001	10 (33.3%)	<0.001
Prevalence of cPAD [n (%)]	46 (93.9%)	32 (66.7%)	<0.001	8 (26.7%)	<0.001
Prevalence of cPAD with stenosis[c] [n (%)]	7 (14.3%)	2 (4.2%)	n.s.	1 (3.3%)	n.s.
Prevalence of pPAD [n (%)]	47 (95.9%)	34 (70.8%)	<0.001	7 (23.3%)	<0.001
Fontaine classification			<0.01		<0.001
Stage 0 [n (%)]	2 (4.1%)	14 (29.2%)		23 (76.7%)	
Stage I [n (%)]	37 (75.5%)	26 (54.2%)		6 (20.0%)	
Stage IIa [n (%)]	6 (12.2%)	6 (12.5%)		1 (3.3%)	
Stage IIb [n (%)]	3 (6.1%)	2 (4.2%)		0 (0%)	
Stage III [n (%)]	1 (2%)	0 (0%)		0 (0%)	
Stage IV [n (%)]	0 (0%)	0 (0%)		0 (0%)	

Notes. [a]PF-ILD vs. nPF-ILD; [b]overall intergroup difference; [c]≥50% according to the NASCET definition. PF-ILD: progressive-fibrosing interstitial lung disease; nPF-ILD: non-progressive-fibrosing interstitial lung disease; ABI: ankle-brachial index; PAD: peripheral arterial disease; cPAD: cerebrovascular peripheral arterial disease; pPAD: peripheral arterial disease of lower limb arteries.

patients with PF-ILD (180.47±39.76 mg/dl) in contrast to nPF-ILD (203.37±47.90 mg/dl; $p<0.05$) and controls (203.10±31.39 mg/dl; $p<0.05$), and HbA_{1c} was higher in both patients with PF-ILD (5.97±0.88%) and nPF-ILD (5.81±0.94%) compared to controls (5.36±0.35%; $p<0.05$). However, all mean HbA_{1c} values were within reference range (<6%). No significant differences occurred for HDL and LDL. The level of inflammation, as shown by CRP and IL-6 levels, was upregulated in ILD patients. CRP was significantly higher in patients with PF-ILD (11.07 ±13.79 mg/l) compared with nPF-ILD (6.16±9.44 mg/l; $p<0.05$) and controls (2.58±3.59 mg/l; $p<0.01$). Differences in IL-6 were even more distinct. Here too, patients with PF-ILD presented with the highest values (8.61±7.23 pg/ml) in contrast to nPF-ILD (4.52±3.77 pg/ml: $p<0.001$) and controls (2.53±1.54 pg/ml; $p<0.001$) patients. The complete results of the blood tests are available in ESM 3.

Lung-function testing, CO-diffusion analysis and six minute walk test

The results of these tests are illustrated in ESM 4. Patients with ILD, especially PF-ILD patients, presented with significantly reduced lung volumes as well as reduced CO-diffusion capacity and coefficient. O_2 support was necessary in 12 patients with PF-ILD and two patients with nPF-ILD ($p<0.001$). PF-ILD was accompanied by a significantly reduced maximum distance during the 6MWT (275±178 m) compared to control (506±97 m; $p<0.001$) and nPF-ILD patients (434±94 m; $p<0.001$).

Prevalence of PAD, pPAD, cPAD and vascular strain analysis

Standard angiological diagnostics

Frequencies of cPAD (80.4% vs. 26.7%, $p<0.001$), pPAD (83.5% vs. 23.3%, $p<0.001$) and PAD in general (86.6% vs. 33.3%, $p<0.001$) were significantly higher in patients with ILD compared to controls. After subdivision of the entire ILD collective into PF-ILD and nPF-ILD patients, the following results were obtained:

Table II shows the prevalence of PAD, pPAD, cPAP and their distribution over Fontaine stages without adjustment for age. PAD in general was present in all patients with PF-ILD (100%) and 73% of patients with nPF-ILD ($p<0.001$). cPAD and pPAD were significantly more frequent in PF-ILD compared to nPF-ILD (both with $p<0.001$) and controls (both with $p<0.001$) (Figure 1).

By performing an adjustment for age via regression analysis, the three groups showed significant differences in the prevalence of pPAD ($p<0.001$) with the odds of developing pPAD increasing by a factor of 71.22 (12.55–404.11) in PF-ILD compared to controls and by a factor of 14.86 (4.17–53.00) in nPF-ILD compared to controls. The prevalence of cPAD was also significantly different between the groups with $p<0.001$ and an OR of 38.69 (8.33–179.81) when comparing PF-ILD patients with the control group and an OR of 10.32 (3.02–35.27) between nPF-ILD patients and the control group. Subsequently, these results were mirrored by the simplified Fontaine classification (as described in chapter 2.5.). As for PAD in general, an adjusted regression analysis could not be performed since all PF-ILD patients were affected. Despite a numerical higher prevalence of PAD, pPAD, and cPAD as well as mean Fontaine classes in PF-ILD, the patients showed no significant difference between PF-ILD and nPF-ILD after adjusting for age. The adjusted regression analyses for pPAD, cPAD and simplified Fontaine classification are presented in Tables III, IV and V.

Discussion

In the general population, the prevalence of PAD is estimated to be 3–10% of people. With over 70 years of age,

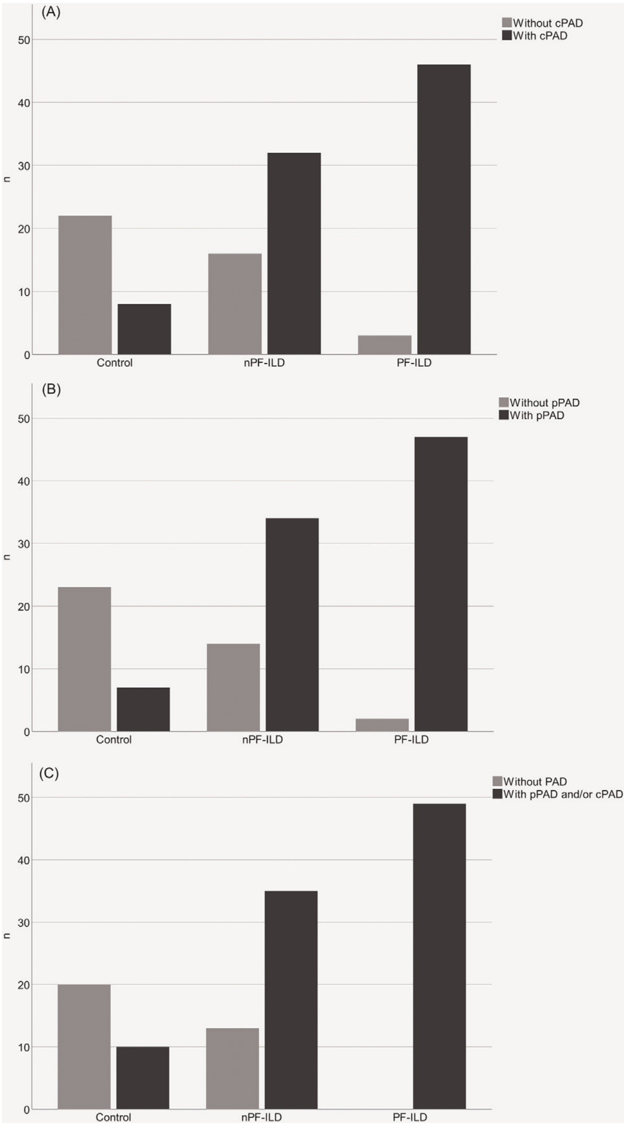

Figure 1. Frequencies of cPAD (A), pPAD (B), and PAD in general (C). *PAD:* peripheral artery disease; *cPAD:* PAD of cervical arteries; *pPAD:* PAD of lower limb arteries; *nPF-ILD:* non-progressive fibrosing interstitial lung disease; *PF-ILD:* progressive fibrosing interstitial lung disease.

the prevalence is increasing to 15–20% [18, 19]. The prevalence of PAD in patients with ILD has been considered to be between 3.6 and 20.0% [6, 8, 9] up to now and, therefore, within the expected frequency of PAD in the general population. These current results indicate, however, that this estimate may need to be revised. Our study revealed a remarkably high atherosclerotic burden in patients with ILD, especially in patients with PF-ILD. Amongst these, every participant presented with atherosclerotic lesions in either carotid or lower-limb arteries. Although age was found to be a confounding factor that was able to explain the more severe affection of PF-ILD compared to nPF-ILD patients, these results are striking and put ILD close to other pulmonary diseases with high rates of comorbid atherosclerosis, such as COPD [11] or obstructive sleep apnoea [10]. According to present data, ILD is an independent risk factor for the presence of atherosclerotic lesions documented via CCDS. It is to discuss that most patients

Table III. Age-adjusted logistic regression model: pPAD

	OR (CI)	*p*
Overall intergroup difference		<0.001
PF-ILD vs. Control	71.22 (12.55–404.11)	
nPF-ILD vs. Control	14.86 (4.17–53.00)	
PF-ILD vs. nPF-ILD	4.79 (0.93–24.60)	
Age	1.09 (1.05–1.15)	<0.001

Notes. pPAD: peripheral arterial disease of lower limb arteries; PF-ILD: progressive-fibrosing interstitial lung disease; nPF-ILD: non-progressive-fibrosing interstitial lung disease; OR: odds ratio; CI: confidence interval.

with ILD presented with asymptomatic, subclinical PAD. However, subclinical PAD has also proven to elevate the cardiovascular risk substantially [20]. Moreover, most patients with ILD, PF-ILD in particular, are suffering from severe dyspnoea which primarily limits their walking distance (cf. ESM 3). During 6MWT exertional dyspnoea limited the walking especially of those patients depending on oxygen support. Therefore, the number of symptomatic patients may be underestimated.

Atherosclerosis is a multifactorial disease that is initiated by LDL accumulation in the arterial wall and sustained and mediated by various drivers, such as smoking habits, diabetes, hypertension, sex, age and systemic inflammation [21, 22]. Eventually, atherosclerosis arises from a mismatch between pro- and contra-atherogenic factors. To interpret the findings of this study, the present results need to be put in the context of atherogenesis and its main drivers: classic cardiovascular risk factors on the one hand and systemic inflammation on the other.

Cardiovascular risk factors in ILD have already been described in detail: According to Schwarzkopf et al. (2018), ILD is accompanied by a relevant burden of cardiovascular risk factors, such as arterial hypertension with and without complications (66.2%), chronic pulmonary diseases (55.9%) and diabetes, with and without complications (31.2%) [5]. Raghu et al. (2015) reported a prevalence of diabetes in patients with IPF between 10% and 32.7%. The prevalence of arterial hypertension ranged from 14% to 71%, and the frequency of hypercholesterolemia varied from 6% to 53% [6]. Both meta-analyses reported higher numbers for males and for advanced age. These data were mirrored in present sample by all groups without significant intergroup difference, except for age, representing a high-risk collective of developing atherosclerosis. Amongst high-risk patients increased prevalence of PAD, up to 40%, can be expected [23]. This expectation was met by the control group in our sample; however, it still is greatly below the prevalence rate of PAD in ILD patients from this study. Therefore, the cardiovascular risk profile alone of patients with ILD does not provide a sufficient explanation for their high atherosclerotic burden.

In this study, patients with ILD presented with significantly elevated levels of CRP and IL-6, both signs of systemic inflammation. The concentration of IL-6 was also significantly higher in patients with PF-ILD compared to nPF-ILD as well as control patients. This study has not been

Table IV. Age-adjusted logistic regression model: cPAD

	OR (CI)	*p*
Overall intergroup difference		<0.001
PF-ILD vs. Control	38.69 (8.33–179.81)	
nPF-ILD vs. Control	10.32 (3.02–35.27)	
PF-ILD vs. nPF-ILD	3.75 (0.90–15.60)	
Age	1.10 (1.06–1.16)	<0.001

Notes. cPAD: cerebrovascular peripheral arterial disease; PF-ILD: progressive-fibrosing interstitial lung disease; nPF-ILD: non-progressive-fibrosing interstitial lung disease; OR: odds ratio; CI: confidence interval.

Table V. Age-adjusted ordinal regression model: Fontaine classification*

	OR (CI)	*p*
Overall intergroup difference		<0.001
PF-ILD vs. Control	21.70 (6.79–69.38)	
nPF-ILD vs. Control	12.64 (4.14–38.62)	
PF-ILD vs. nPF-ILD	1.73 (0.70–4.21)	
Age	1.06 (1.03–1.10)	<0.001

Notes. *Simplified classification as described in chapter "Statistical analysis". PF-ILD: progressive-fibrosing interstitial lung disease; nPF-ILD: non-progressive-fibrosing interstitial lung disease; OR: odds ratio; CI: confidence interval.

designed to explain atherogenesis in ILD. However, an analogy to other pulmonary diseases with high atherosclerotic burden can be discussed. Here, an association with atherosclerosis due to activated inflammatory pathways is well-known and has been the subject of several investigations. For example, COPD is accompanied by an elevated cardiovascular risk [24]. This is mediated not only by smoking, which is a common risk factor for both diseases, but systemic inflammation. Although the pathology is still not completely understood, current knowledge suggests that cigarette smoke induces an upregulation of IL-6 and tumour necrosis factor alpha (TNFα), resulting in self-sustaining systemic inflammation and a proatherogenic environment [25, 26]. Patients with OSA seem to be even more severely affected [10]. Here too, the pathogenesis remains under study. Most likely, nightly intermittent hypoxemia (IH) and reoxygenation induce several proatherogenic pathways: Locally, increasing levels of reactive oxygen species (ROS) promote oxidative stress and endothelial dysfunction. Systemically, intermittent hypoxemia leads to higher levels of IL-6 and, consecutively, TNFα, CRP, hypoxia-inducible-factor (HIF) 1, and activation of nuclear factor kappaB pathway (NF-κB) [26, 27, 28]. Therefore, systemic inflammation seems to play a pivotal role in comorbid atherogenesis in pulmonary diseases.

In summary, the pathogenesis of atherosclerosis in ILD is still not fully understood. Most likely, the combination of a high cardiovascular risk profile and systemic inflammatory processes, similar to those in patients with OSA or COPD, may be responsible for atherogenesis in ILD.

PAD still is associated with a high five-year mortality of up to 25% and is considered to be a more severe manifestation of atherosclerosis compared to CAD alone. This increased risk is attributed to higher levels of systemic inflammation and higher burden of cardiovascular risk factors [29]. In this context, the common presence of PAD in patients with ILD, surely is one explanation for the high mortality rate of ILD patients and an indicator of systemic inflammation induced by pulmonary fibrosis.

Limitations

This study is mostly limited by its sample size. Distribution of ILD-causing diseases, especially IPF, differed significantly throughout ILD groups, therefore the results with regard to PF-ILD possibly are biased by IPF patients. Although there were no significant differences with regard to the baseline characteristics (except for age), distribution of packyears, prevalence of diabetes and/or prevalence of COPD may have influenced the present results, as they all are connected to atherogenesis. This study was further limited by the methods, as CCDS was used to verify the presence of atherosclerotic lesions, whereas data on prevalence of PAD in the general population mostly relies on ABI. The number of symptomatic patients may have been underestimated due to reduced walking speed due to exertional dyspnoea.

Larger studies or register analyses, including angiological surveillance, are needed to confirm the present results.

Conclusions

This study provides the first evidence that ILD is an independent risk factor for PAD. PAD seems to be generally present in ILD patients and is associated with increased five-year mortality. Therefore, the high mortality rate of ILD patients may also be attributed to PAD. Patients should be screened for PAD when diagnosed with ILD, and PF-ILD in particular. Secondary prevention, lipid-lowering therapy, and regular re-examinations should be recommended in this context.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a001068

ESM 1. Classification of PAD according to Fontaine stages and Rutherford grades and categories (Table)

ESM 2. Medication (Table)

ESM 3. Results of blood testing (Table)

ESM 4. Lung functioning and six-minute-walking- exercise (Table)

References

1. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459–544.
2. Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, Sanyal S, Brillet P-Y, Brauner M, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J. 2017;50(2):1602419.
3. Olson A, Hartmann N, Patnaik P, Wallace L, Schlenker-Herceg R, Nasser M, et al. Estimation of the Prevalence of Progressive Fibrosing Interstitial Lung Diseases: Systematic Literature Review and Data from a Physician Survey. Adv Ther. 2021;38:854–67.
4. Cottin V, Hirani NA, Hotchkin DL, Nambiar AM, Ogura T, Otaola M, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27(150):180076.
5. Schwarzkopf L, Witt S, Waelscher J, Polke M, Kreuter M. Associations between comorbidities, their treatment and survival in patients with interstitial lung diseases – a claims data analysis. Respir Res. 2018;19(1):73.
6. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. Eur Respir J. 2015;46:1113–30.
7. Clarson LE, Bajpai R, Whittle R, Belcher J, Abdul Sultan A, Kwok CS, et al. Interstitial lung disease is a risk factor for ischaemic heart disease and myocardial infarction. heart. 2020;106:916–22.
8. Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwyler J, Oltmanns U, Muley T, et al. Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. PLoS One. 2016;11:e0151425.
9. Behr J, Kreuter M, Hoeper MM, Wirtz H, Klotsche J, Koschel D, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. Eur Respir J. 2015;46:186–96.
10. Stumpf MJ, Schaefer CA, Krycki J, Schueler R, Pizarro C, Nickenig G, et al. Impairment of vascular strain in patients with obstructive sleep apnea. PLoS One. 2018;13:e0193397.
11. Pizarro C, Linnhoff F, van Essen F, Pingel S, Schaefer CA, Schahab N, et al. Lower extremity and carotid artery disease in COPD. ERJ open research. 2016;2(4):00037–2016.
12. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718–27.
13. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324–43.
14. Nagata K, Tomii K, Otsuka K, Tachikawa R, Otsuka K, Takeshita J, et al. Evaluation of the chronic obstructive pulmonary disease assessment test for measurement of health-related quality of life in patients with interstitial lung disease. Respirology. 2012;17:506–12.
15. Danesh J, Erqou S, Walker M, Thompson SG, Tipping R, Ford C, et al. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. Eur J Epidemiol. 2007;22:839–69.
16. Naqvi TZ, Lee M-S. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging. 2014;7:1025–38.
17. Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. Vasa. 2019;48:1–79.
18. Diehm C, Schuster A, Allenberg JR, Darius H, Haberl R, Lange S, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis. 2004;172:95–105.
19. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985;71:510–5.
20. Sartipy F, Garcia Pereira Filho AJ, Lundin F, Wahlberg E, Sigvant B. Presence of asymptomatic peripheral arterial disease in combination with common risk factors elevates the cardiovascular risk substantially. Int J Cardiol Cardiovasc Risk Prev. 2022;13:200130.
21. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5:56.
22. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019;7: e1020–e1030.
23. Si S, Golledge J, Norman P, Nelson M, Chew D, Ademi Z, et al. Prevalence and outcomes of undiagnosed peripheral arterial disease among high risk patients in Australia: An Australian REACH sub-study. Heart Lung Circ. 2019;28:939–45.
24. Cavaillès A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. Eur Respir Rev. 2013;22:454–75.
25. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of "overspill" of inflammatory mediators from the lungs? Review of the evidence Thorax. 2010;65:930–6.
26. Hughes MJ, McGettrick HM, Sapey E. Shared mechanisms of multimorbidity in COPD, atherosclerosis and type-2 diabetes: the neutrophil as a potential inflammatory target. Eur Respir Rev. 2020;29:190102.
27. O'Dea E, Hoffmann A. NF-κB signaling. Wiley Interdiscip Rev Syst Biol Med. 2009;1:107–15.
28. Jain T, Nikolopoulou EA, Xu Q, Qu A. Hypoxia inducible factor as a therapeutic target for atherosclerosis. Pharmacol Ther. 2018;183:22–33.
29. Belch JJF, Brodmann M, Baumgartner I, Binder CJ, Casula M, Heiss C, et al. Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease. Vasa. 2021;50: 401–11.

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Conflict of Interest
The authors declare that no competing interests exist regarding this work.

Authorship
Conceptualization: MJS, DS, CAS and CP; methodology: MJS, DS, CAS and CP; data acquisition: MJS, MFF, MMLW and LB; software: MJS, LW and GN; statistical analysis and data curation: MJS and LW; validation: MJS, DS, CAS and CP; resources: NS, LW, DS and GN; writing–original draft: MJS and MFF; writing–review editing: MJS, MFF, MMLW, LB, LW, CAS and CP. All authors have read and agreed to the published version of the manuscript.

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ORCID
Max Jonathan Stumpf
https://orcid.org/0000-0003-4558-1833
Max Fabian Fleddermann
https://orcid.org/0000-0002-1736-9635
Leonie Biener
https://orcid.org/0000-0002-8132-7958
Leonie Weinhold
https://orcid.org/0000-0002-9194-9427
Dirk Skowasch
https://orcid.org/0000-0003-2377-5936
Carmen Pizarro
https://orcid.org/0000-0002-2386-4325

Correspondence address
Dr. med. Max Jonathan Stumpf
University Hospital Bonn
Venusberg-Campus 1
53127 Bonn
Germany

max.stumpf@ukbonn.de

Letter to the editor

A potentially dangerous complication of ovarian vein embolization for pelvic congestion syndrome treatment

Gabor Forgo[1], Stefano Barco[1], Valdrin Kuci[1], Matthias Walting[2], and Nils Kucher[1]

[1] Department of Angiology, University Hospital Zurich, Switzerland
[2] Department of Surgery, Lucerne Cantonal Hospital, Switzerland

Introduction

Chronic pelvic pain (CPP) is characterized by continuous or intermittent lower abdominal or pelvic pain lasting more than 6 months. It is a common health problem among women leading to a significant economic burden worldwide [1]. The prevalence of CPP ranges between 6% and 24%, with pelvic venous disorders (PeVD) being one of the most frequent causes [2].

Pelvic vein insufficiency in women can originate from the left (or more rarely right) ovarian and internal iliac veins. In this report we describe a case of PeVD caused by a suspected flow reversal (reflux) in the left ovarian vein, previously described as pelvic congestion syndrome (PCS).

PCS is typically diagnosed in women with a history of pregnancy experiencing typical symptoms, such as CPP worsened by prolonged standing and/or menstruation and sexual intercourse [3].

If PCS is suspected, it can easily and safely be treated with minimally invasive methods, which improve symptoms in most patients [4, 5].

We report a potentially dangerous and so far not described complication of endovascular PCS treatment.

Clinical presentation

A 40-year old female patient was referred to our department with a suspected PCS. Chief complaints were CPP, vulvar varicosity and dyspareunia. The patient had 2 children.

The medical history otherwise included a laparoscopic hysterectomy with salpingectomy on both sides and ovarectomy on the right due to endometriosis and cystic deformities 3 years before.

The initially performed MR-phlebography showed a dilated ovarian vein on the left with a maximum diameter of 8 mm (Figure 1) and pelvic varicosities. Based on these findings and the typical symptoms for PCS, the patient was offered a diagnostic phlebography. The phlebography showed a dilated ovarian vein (Figure 2) with reflux on the left with sufficient collateral circulation. Subsequently, an embolization with polidocanol (aethoxysklerol 3%) and coiling was carried out. After the intervention, the patient experienced some abdominal discomfort but was discharged with Ibuprofen as needed. Due to the increasing pain in the lower abdomen and vomiting after discharge, the patient visited the emergency department 2 days later. The laboratory findings showed raised inflammatory markers. Consequently, a CT-scan showed an enlarged ovary on the left (Figure 3). Due to persisting abdominal symptoms and increasing inflammatory markers the indication for a laparoscopy was given. Intraoperatively a massive enlarged and hemorrhagic left ovary was seen (Figure 4) and an emergency ovarectomy was performed. The diagnosis of a hemorrhagic ovarian necrosis was made.

After the emergency ovarectomy on the left side the acute symptoms of the patient resolved completely but CPP and dyspareunia are persistent.

Discussion

The standard treatment of PCS is typically endovascular, according to clinical practice guidelines. Generally, ovarian vein reflux is visualized during phlebography and treated simultaneously with embolization using a combination of coils and foam sclerotherapy, or, alternatively, an occlusion device.

Most commonly reported complications are coil migration, allergic reaction to contrast dye, transient abdominal pain, and vein perforation [4]. Ovarian necrosis is a previously unreported complication of such a procedure.

The most likely cause of this complication is due the outflow obstruction after the embolization. In this patient with prior hysterectomy as well as bilateral salpingectomy and

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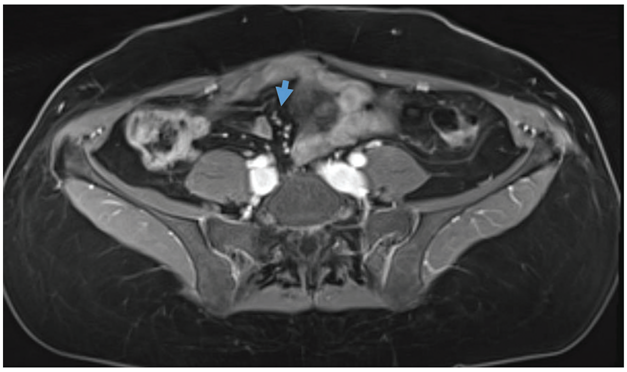

Figure 1. A dilated left ovarian vein (arrowhead) on MR-phlebography, observed in loco typico anterior to the psoas muscle.

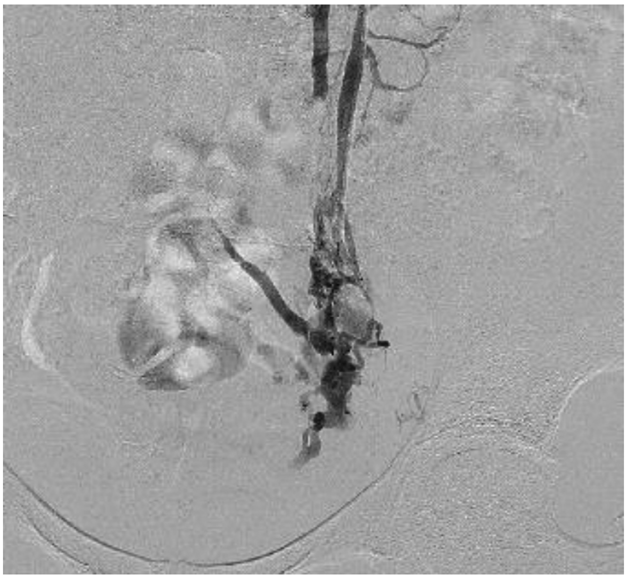

Figure 2. Selective imaging of the left ovarian vein and pelvic varicosities during phlebography. A flow reversal (reflux) was suspected.

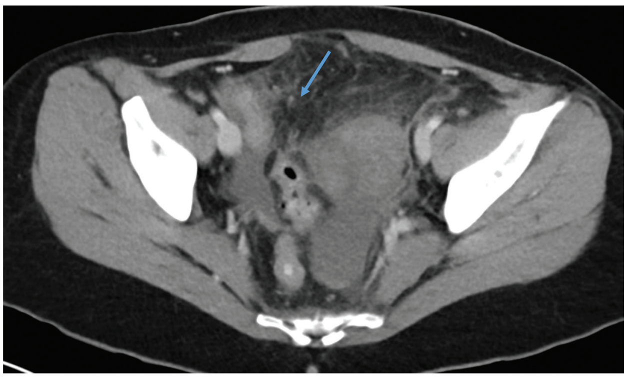

Figure 3. Severely enlarged (5.8×5.3×5cm) left ovary without contrast enhancement and adjacent fat tissue imbibition on CT-scan with venous sequence.

ovarectomy on the right side, the left ovarian vein represented the only outflow vein. The therapeutic occlusion of this vein led to vascular congestion and subsequent hemorrhagic necrosis.

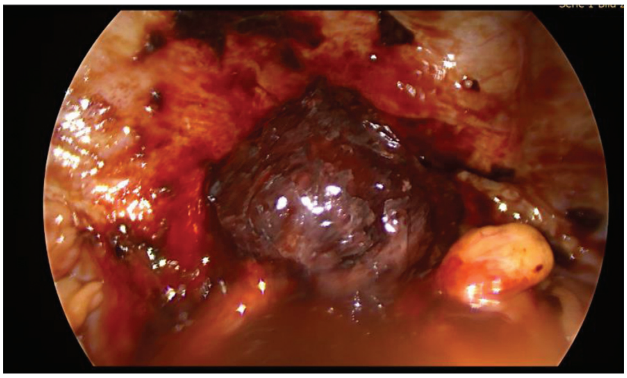

Figure 4. Enlarged and hemorrhagic left ovary during emergency laparoscopy.

In conclusion, in suspected PCS, with the ovarian vein being the only outflow vein the flow reversal must be assessed carefully before embolization.

References

1. Riding DM, Hansrani V, McCollum C. Pelvic vein incompetence: clinical perspectives. Vasc Health Risk Manag. 2017;13:439–47.
2. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. Pain Physician. 2014;17(2):E141–7.
3. Jeanneret C, Beier K, von Weymarn A, Traber J. Pelvic congestion syndrome and left renal compression syndrome - clinical features and therapeutic approaches. Vasa. 2016;45(4):275–82.
4. Neuenschwander J, Sebastian T, Barco S, Spirk D, Kucher N. A novel management strategy for treatment of pelvic venous disorders utilizing a clinical screening score and non-invasive imaging. Vasa. 2022;51(3):182–9.
5. Reinboldt-Jockenhöfer F, Traber J, Holzer LI, von Weymarn A, Dissemond J, Duewell S, Impact of ovarian vein embolization in recurrent varicose veins of the lower extremity. Vasa. 2022; 51(4):212–21. https://doi.org/10.1024/0301-1526/a001008

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ORCID
Gabor Forgo
https://orcid.org/0000-0003-0810-750X

Correspondence address
Dr. Gabor Forgo, MD
University Hospital Zurich: Universitätsspital Zürich
Raemistrasse 100
8091 Zürich
Switzerland

gabor.forgo@usz.ch

