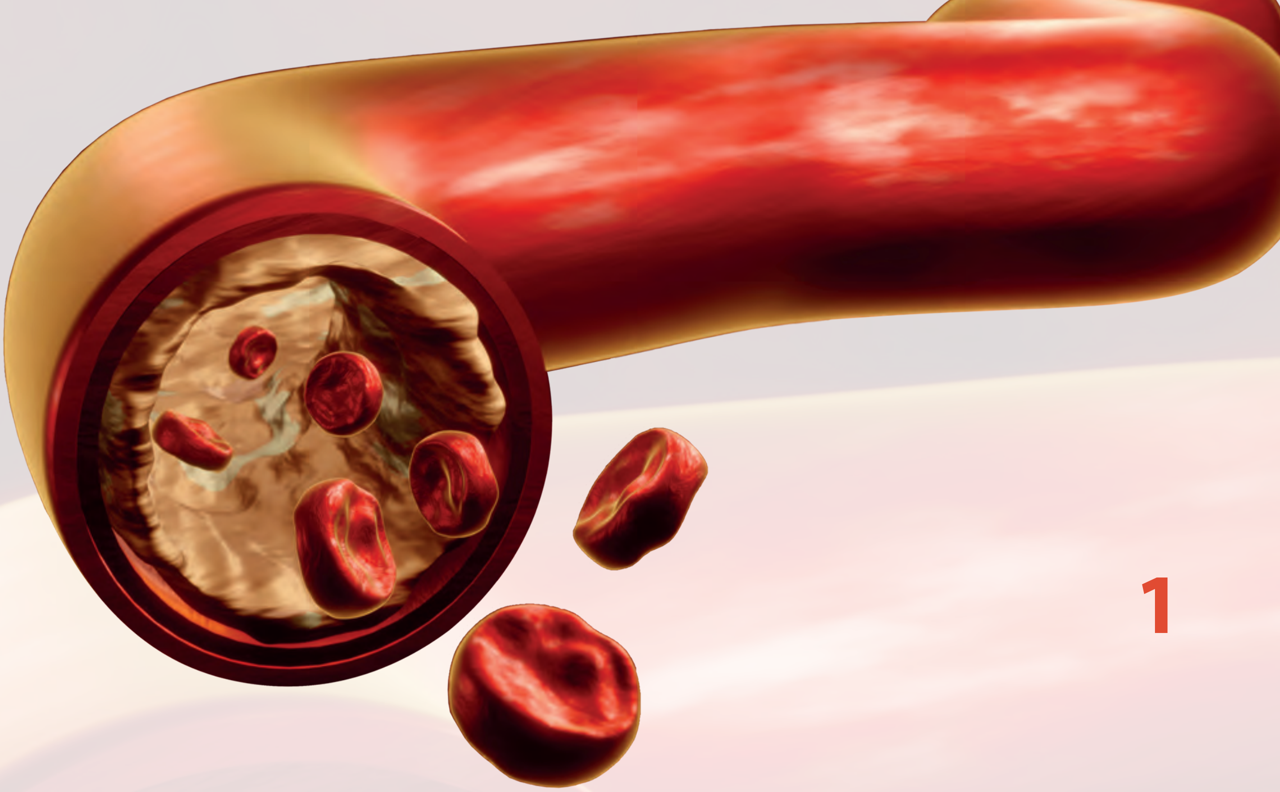

1

INTRODUCTION

Gergana T. Taneva, Konstantinos P. Donas

A total of 236 million people were estimated to suffer from peripheral artery disease (PAD) worldwide in 2015, and numbers have been rising since then.[1, 2] The overall prevalence of lower extremity PAD varies, depending upon the studied population. Since the global population is aging and due to the fact that PAD is strongly age-related, it is estimated to become increasingly prevalent in the future.[1] PAD prevalence reaches 20% in a population older than 70 years, leading to severe deterioration in the functional status in a quarter of the cases.[3, 4] Several comorbidities are frequently concomitant (*e.g.*, diabetes, dyslipidemia, chronic renal insufficiency) in PAD patients.[5] Patients with PAD display a wide range of clinical status. Although asymptomatic in the majority of cases (50%), 10-35% present claudication while 2-5% present with critical limb-threatening ischemia (CLTI).[6] Major amputation is rare (3% at 5 years and 10% at 15 years),[4, 7] increasing the risk by 5- to 10-fold in diabetic patients.[4] PAD patients with claudication eventually develop CLTI with an amputation-free survival rate limited to 45% at 1 year.[3, 4]

The lesion features, such as the anatomical location (above *versus* below the knee), lesion characteristics (chronic total occlusions [CTOs] *vs.* stenosis), and lesion morphology (fibrotic *versus* highly calcified, etc.) influence the treatment planning, aim, and ability to access and deliver the therapy and susceptibility to restenosis.[8] The femoropopliteal arteries are most commonly affected.[7] As we progress, distally arterial calcification increases in patients with PAD.[9] While above the knee vessels (4-9 mm) present mixed plaque morphology with multiple plaque types and thrombus content, the smaller below the knee vessels (1.5-3.5 mm) present highly calcified and tortuous anatomy,[9, 10] being approximately 42% of lesions CTOs.[11] CTOs increase the risk for restenosis after endovascular treatment.[12]

In an aging population with a rising incidence of PAD, endovascular therapy is a favorable alternative to open surgical bypass.[13] As a minimally invasive approach, endovascular therapy incurs less physiological stress and periprocedural complications.[13] Thus, an endovascular-first approach is usually recommended in femoropopliteal occlusive disease.[4]

Today, we are witnessing rapid progress and evolution of endovascular technologies, leading to the treatment of highly complex and long PAD lesions. The mechanisms of endovascular therapy have evolved beyond pneumatic dilation, forcing plaque against the vessel wall with angioplasty and stenting.[13] Despite the advances in the endovascular treatment for short-segment occlusive disease, postprocedural patency for long-segment and highly calcified lesions remains challenging in the femoropopliteal region.[13] Vessel calcification remains an important burden to lesion crossing and dilation, beholding risk for recoil, dissection, and reconstruction failure.[14] Calcification in the femoropopliteal arteries is found in 47% to 72% of PAD patients.[14] Lesion calcification burdens the current endovascular treatment of PAD not only at the treatment level, but also at diagnostic and scaling systems levels.

In the present book, we intend to summarize - in a comprehensive and reader-friendly way - the modern endovascular techniques and modalities, with a proven use of the treatment of highly calcified femoropopliteal lesions. In the first chapters we focus on currently available diagnostic tools, such as intravascular ultrasound and carbon dioxide angiography. Then, we develop several lesion preparation modalities, drug-eluting balloons and scaffolding as treatment options to then, finalize with updated possible treatment algorithms. The here presented data is based on the currently available armamentarium for PAD treatment, focusing on anatomical and patient-specific characteristics. Authors with international influence have contributed writing several of the here presented chapters. The choice of the presented tools and content of the book is mainly based on the authors' experience with those systems, without implying that other devices and modalities not mentioned in this book may have comparable or even superior performance on challenging calcified lesions of the femoropopliteal region.

In general, awareness of the currently available technologies to properly face the challenge of vessel calcification in PAD patients is paramount for the effective, updated, and individualized treatment of each case. We hope that the present work would result amenable, useful, and enriching for the reader, possibly supporting the best selection of treatment for your patients, and after all, improving the vascular care for PAD patients.

Sincerely, the authors of the book.

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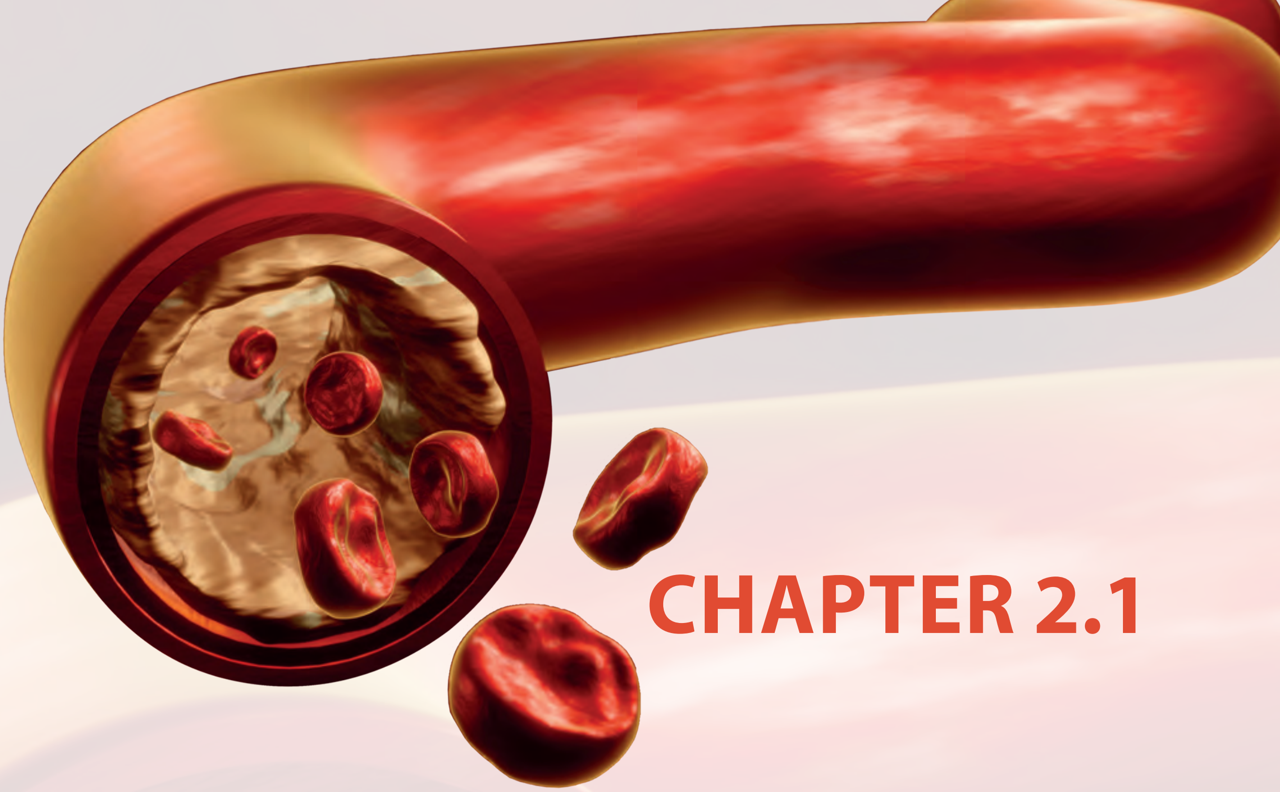

CHAPTER 2.1

ALTERNATIVE AND COMPLEMENTARY DIAGNOSTIC MODALITIES

Use of intravascular ultrasound in peripheral arterial disease

Konstantinos P. Donas

Intravascular ultrasound (IVUS) catheters are currently manufactured by two major companies, Boston Scientific (Boston Scientific, Marlborough, MA, USA) and Philips (Philips, Amsterdam, the Netherlands) after their acquisition of Volcano Corporation (San Diego, CA, USA) in 2015. The catheter sizes range from 2 to 4 Fr and can be easily guided through a 5 and 6 Fr femoral sheath. Larger IVUS catheters are also used for larger peripheral vessel applications and require 8 Fr sheaths.

IVUS uses a piezoelectric transducer located at the tip of the catheter that generates sound waves when electrically stimulated. These waves propagate into different tissues and thus produce a reflection image based on the acoustic properties of that tissue. The transducer is found in two different designs: 1) the mechanical single rotating device; and 2) the electronic-phased array device (several non-rotating transducers present at the tip of the catheter and activated sequentially).[1-3]

Early IVUS imaging was in grayscale and plaque morphology was classified based on visual appearance by comparing the echogenicity of the plaque to its surrounding adventitia. This has been possible with the use of 20-40 MHz transducers. The plaques were classified into soft plaque, fibrous plaque, calcified modalities, and mixed type.[1-3]

Nowadays IVUS characteristics have contributed to its development as an important adjunctive modality for peripheral endovascular procedures because of its ease and accuracy in determining different imaging parameters, including luminal cross-sectional measurements and accurate information about lesion morphology such as true vessel diameters, wall thickness/layers, length, shape, and volume of lesion, the position of a lesion within the lumen (concentric or eccentric), type of lesion (fibrous, necrotic, calcified and mixed), any presence and extent of an intimal flap, arterial dissection, plaque ulceration, presence and volume of thrombus.[1-3] IVUS does not only provide diagnostic information, but it may also guide the choice of the appropriate treatment method, assist in the accurate deployment of an endovascular device, and check the efficiency of the procedure. Lofrey *et al.* published in 2020 an updated overview of the published evidence on IVUS in the treatment of peripheral arterial disease (PAD).[4]

IVUS in combination with angioplasty/stenting

Four studies with retrospective design investigated a total number of 2,258 patients comparing percutaneous transluminal angioplasty (PTA) and stenting for PAD treatment with or without the use of IVUS.[5-8] The long-term patency rates ranged from 62 to 100% in the IVUS group *vs*. 69% to 83.4% in the non-IVUS group.

Iida *et al.*[6] investigated the efficacy of IVUS in femoropopliteal stenting for PAD with TASC II class A to C lesions. The authors found a statistically significant difference in favor of the IVUS group in a total of 468 patients. Indeed, IVUS use was associated with a significantly higher 5-year primary patency (65±6% *vs*. 35±6%, P<0.001) rate, better freedom from any adverse limb event rate (P<0.001), and better event-free survival rate (P<0.001).[5-8]

IVUS in combination with atherectomy

One prospective earlier study assessed the use of IVUS in combination with directional atherectomy in a population of 30 patients showing an encouraging 100% technical success rate.[9] The long-term patency was 90% and clinical success was 100%. There were no periprocedural complications or major amputations in this small patient sample size.

More recently, Krishnan *et al.*[10] retrospectively compared the 1-year outcomes for patients with femoropopliteal in-stent restenosis using directional atherectomy guided by IVUS *vs*. directional atherectomy guided by digital subtraction angiography (DSA). The authors concluded that IVUS in conjunction with directional atherectomy could improve clinically driven target lesion revascularization (CD-TLR) rates for femoropopliteal in-stent restenosis patients by allowing the operator to visualize the lesion more accurately than with DSA minimizing the possible residual stenosis post-directional atherectomy treatment and aggressive debulking (Figure 2.1.1).

IVUS for true-lumen re-entry

Five retrospective studies evaluated IVUS for true lumen re-entry during subintimal PTA.[11-15] The goal of one of these 5 studies was to perform comparisons between true lumen re-entry with and without the use of IVUS.[12] The technical success was higher in the IVUS group (97% *vs*. 81%). It seems like real-time imaging with IVUS enables subintimal tract creation and directed needle deployment. In that sense, the IVUS scanner adds information not only about the intima and the lumen but also confirms vessel patency at the point of the needle due to its color flow capabilities. In the cited studies, the accuracy and controlled re-entry offered by IVUS catheters reduced the risk of dissection-related complications, such as perforations caused by guidewire or catheter malposition, even for thick calcified plaques. Another cited advantage of the IVUS re-entry catheters is the shortened intervention time between

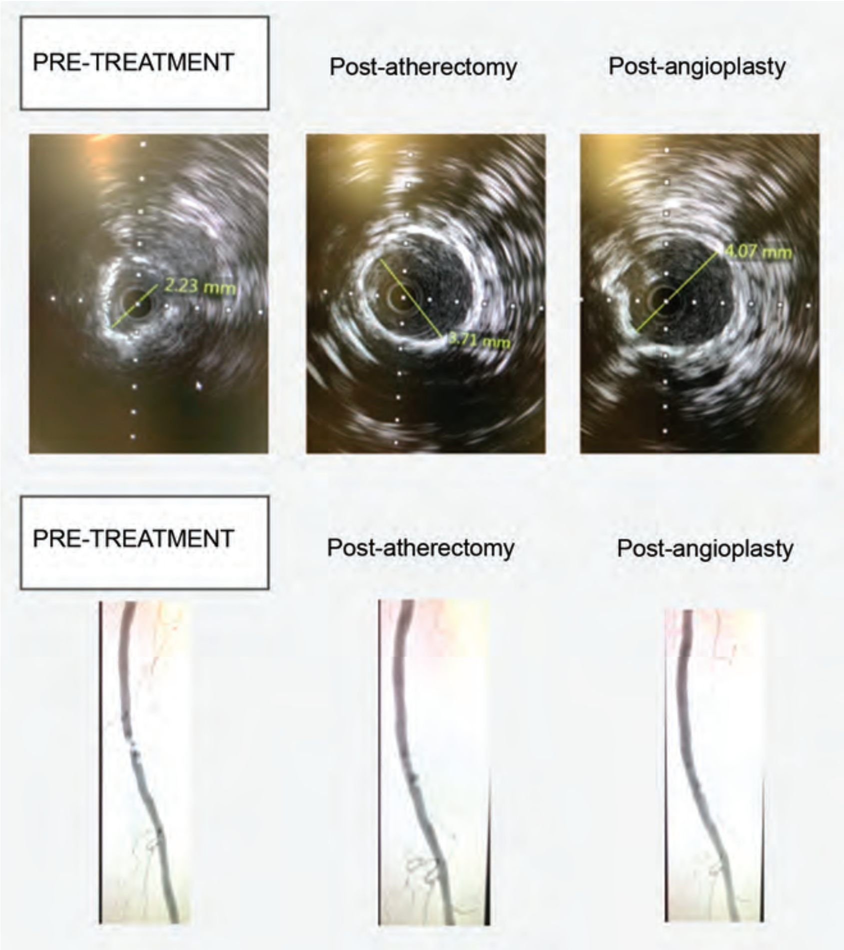

Figure 2.1.1. *A-C) Mid-superficial femoral artery occlusive and calcified lesion: A) before the treatment; B) after atherectomy; and C) after balloon angioplasty. After successful recanalization, digital IVUS Opticross 0.018 system (Boston Scientific) and angiography was used for pretreatment, postatherectomy (Jetstream rotational atherectomy device, Boston Scientific) and post-angioplasty (Ranger drug-eluting balloon, Boston Scientific) evaluation. Case performed at the Department of Vascular and Endovascular Surgery Asklepios Clinic Langen, Langen, Germany.*

3 and 10 minutes, limiting the radiation exposure for the patient and operator while decreasing the risk for periprocedural complications related to a prolonged intervention. In the 5 studies investigating the use of IVUS re-entry devices, no significant periprocedural or post-procedural complications were reported.[11-15]

Conclusions

IVUS has improved fast from a purely diagnostic imaging modality to a very useful adjunctive tool to DSA in the evaluation of vasculature. It may provide a more precise visualization of what happens in the blood vessel and plays an increasing role in peripheral arterial occlusive procedures minimizing the rate of reinterventions. As endovascular procedures become increasingly complex, technical, and clinical successes will be related to the degree of accuracy of the guidance device used during the procedure. IVUS is relatively easy to use and can be widely available. Therefore, IVUS should be part of training programs and the routine practice of all vascular specialists. However, for most of centers, significant costs and expertise in image interpretation might limit its systematic use, at least for now.

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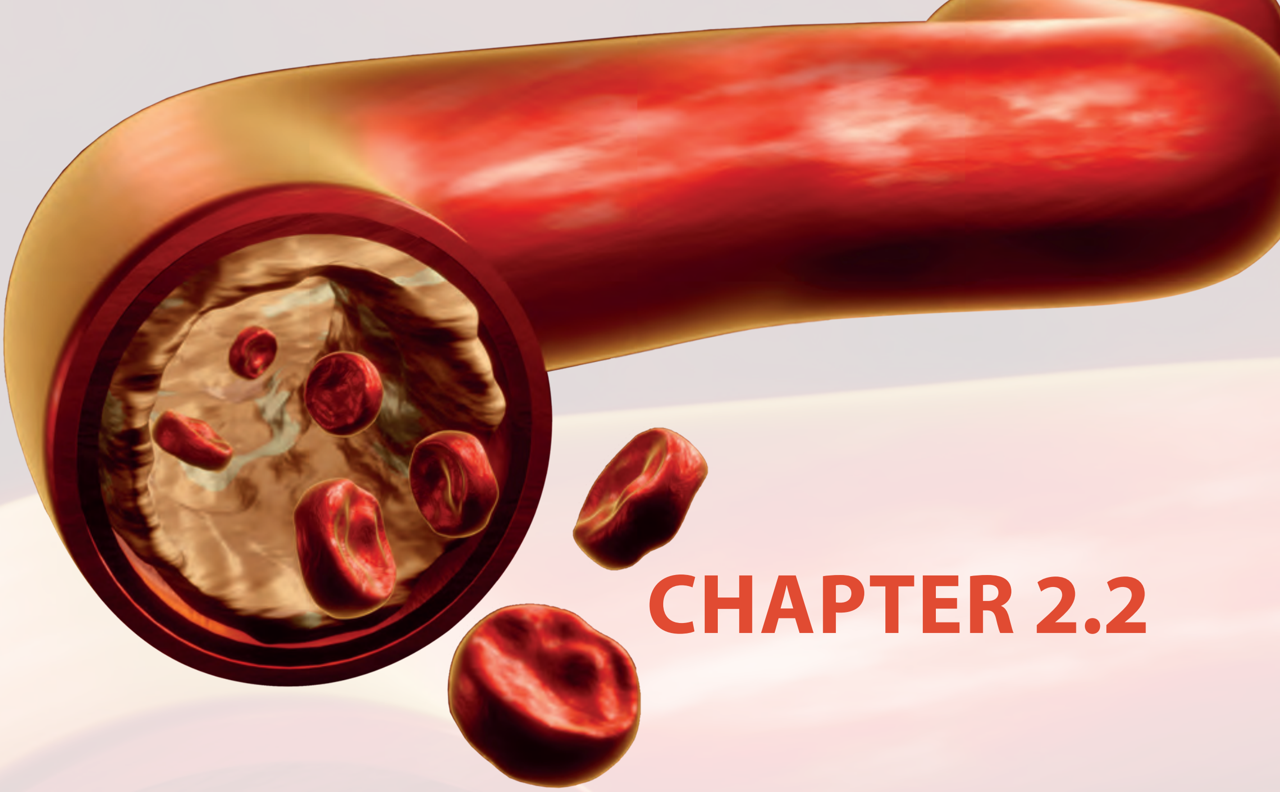

CHAPTER 2.2

Carbon dioxide angiography for peripheral interventions

Georgios I. Karaolanis, Gergana T. Taneva, Konstantinos P. Donas

Peripheral artery disease (PAD) shows rapidly increasing morbidity and mortality during the last years, and it is estimated to affect up to 30% of the elderly primary care population within the following years.[1, 2] This group of patients often has several associated comorbidities, including diabetes mellitus, chronic kidney disease (CKD), and hypertension, which gradually deteriorate the patient's clinical status. When conservative treatment (medication and exercise) does not reduce the symptoms of claudication, and in case of chronic limb-threatening ischemia (CLTI) when the patient is at risk of lower limb amputation, endovascular revascularization is the standard of care.[3] However, endovascular treatment requires the use of an iodinated contrast medium (ICM) to visualize vessel anatomy and malformation (aneurysms, stenosis, etc.), a trend that continues to date with some adverse consequences.[4] CI-AKI (contrast-induced acute kidney injury) represents the most common negative consequence after using ICM, while up to date, there is no global use of an alternative contrast medium without nephrotoxicity.[5-7] However, other patients present history of ICM allergy reactions needing preoperative medication to annulate possible adverse events while somehow burdening the endovascular intervention in the emergent setting.

Carbon dioxide (CO_2) angiography is a diagnostic radiologic procedure proposed more than 50 years ago to obtain vascular images without using ICM.[8, 9] CO_2 safety is a widely discussed topic. ESVS guidelines recommended the use of CO_2 as a contrast medium in PAD imaging of vascular anatomy in patients with an allergy to contrast material or in individuals with severe CKD.[10] In this chapter, we aimed to briefly review the main knowledge based on CO_2 angiography for peripheral interventional angiography.