Mechanisms Underlying Drug Delivery to Peripheral Arteries

Jun Li, MD[a,b], Rami Tzafriri, PhD[c], Sandeep M. Patel, MD[a,b], Sahil A. Parikh, MD, FSCAI[d,*]

KEYWORDS

• Peripheral arterial disease • Drug delivery • Drug-eluting stents • Drug-coated balloons

KEY POINTS

- Despite being a contiguous system, there are drastic architectural, ultrastructural, and biophysiological differences between the coronary and peripheral vascular beds.
- The technologies that have been developed to perfect endovascular revascularization in the coronary artery defies a direct application in the peripheral artery arena.
- An understanding of drug delivery mechanisms and the barriers to absorption is imperative in the development and application of devices in the peripheral arteries.
- Current drug delivery devices available for above-knee targets are broader than for below-knee targets; further studies are necessary to comprehend successful delivery in below-knee arteries.

INTRODUCTION

Peripheral artery disease (PAD) affects an estimated 8.5 million Americans over the age of 40, with a global prevalence of approximately 202 million people.[1] The spectrum of clinical manifestations range from asymptomatic ischemia to exercise-induced claudication to critical limb ischemia (CLI). In patients with PAD, approximately 1% to 3% present with CLI, which still carries with it a high morbidity and mortality rate.[2]

Revascularization remains the cornerstone of therapy for limb salvage in patients with CLI. Moreover, patients with lifestyle-limiting claudication despite guideline-directed medical therapy may undergo revascularization to improve their quality of life and functional status.[1] Endovascular revascularization is a suitable approach in patients with favorable anatomy, as well as for those deemed to be high risk for surgical revascularization, and is frequently considered the first option in patients with both claudication and CLI.

As with all endovascular interventions, the act of dilating the blood vessel with a balloon with or without the additional scaffolding of a stent incites a stereotyped vascular response to injury. The mechanical insult causes a thrombotic

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[a] Division of Cardiovascular Medicine, Department of Interventional Cardiology, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, 11000 Euclid Avenue, Cleveland, OH 44106, USA; [b] Department of Medicine, Case Western Reserve University School of Medicine, 2109 Adelbert Road, Cleveland, OH 44106, USA; [c] CBSET Inc, 500 Shire Way, Lexington, MA 02421, USA; [d] Endovascular Services, Division of Cardiology, Department of Medicine, Center for Interventional Vascular Therapy, Columbia University Medical Center/NY Presbyterian Hospital, Columbia University College of Physicians and Surgeons, 161 Fort Washington Avenue, New York, NY 10032, USA

* Corresponding author.

E-mail address: sap2196@cumc.columbia.edu

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response with both fibrin-rich thrombi and platelet aggregation, an inflammatory response that includes monocyte adherence and macrophage infiltration, recruitment and stimulation of vascular smooth muscle cells (SMCs), and circumferential remodeling, which results in intimal hyperplasia and clinical restenosis.[3] Local elution of antiproliferative drugs from stents and balloons is widely used to help curb this cascade of maladaptive responses while limiting the risk of systemic toxicity.

CORONARY VERSUS PERIPHERAL ARTERIES

Although parallels exist between the coronary and peripheral vasculature and the available technology for revascularization, it should be recognized that there are intrinsic differences between the 2 vascular systems in their underlying architecture. The archetype of the vascular wall has been well described, with 3 layers known as tunicae (intima, media, and adventitia). Each layer contains distinct cells and extracellular matrix constituents (Table 1), which serve to not only provide the differential functions for each layer, but also allows for a synergistic and regulatory partnership between the two.[4,5] The extracellular matrix is a dynamic and unique entity, differing based on the type of vessel it resides in, the specific tunica that it generates, and the injury that is incurred (pressure or flow, mechanical, and biochemical). This autoregulatory mechanism is vital in vertebrates with fully closed circulatory systems owing to the need to (i) accept high-pressure ejection in the larger arteries and (ii) accept large volume changes in the remainder of the arterial tree with little change in pressure.[6] Furthermore, on a macroscopic level, arteries in the periphery are subject to significantly taxing mechanical forces (eg, flexion, torsion, compression, elongation, and contraction), compared with coronary arteries. These considerations should be recognized in the development of tools used for endovascular revascularization for the coronaries and lower extremities alike.[7]

Throughout the history of coronary revascularization, many vital lessons have been learned that may be relevant to peripheral revascularization. First, the mechanism of balloon angioplasty is to induce vessel injury to achieve acute lumen gain. However, angioplasty alone has been plagued with abrupt vessel closure, as well as vessel recoil, resulting in both acute and late lumen loss. The advent of bare metal stents (BMS) was intended to circumvent some of the shortcomings of balloon angioplasty. Despite the ability of BMS to reduce initial adverse events, they remain an imperfect solution for late lumen loss owing to development of in-stent restenosis (ISR; Fig. 1). Drug-eluting stents (DES) were thus introduced as a way to decrease ISR.[8] Despite ongoing advancements aimed at improving DES deliverability, efficacy, and safety to devise the "perfect" stent, stent thrombosis and ISR remain rare but vexing complications.[8,9] Bioresorbable vascular scaffolds (BVS) were developed to curtail the incidence of late ISR and to return vasomotor reactivity to injured vessel, although the first-generation iteration of this technology has been beset by an increased rate of scaffold thrombosis.[10,11]

Comparatively, the narrative on endovascular revascularization of peripheral arteries is still in its infancy. Moreover, the management strategy for 1 peripheral vessel cannot simply be applied to all peripheral vessels (eg, iliacs vs tibial arteries). Experience with drug-coated balloons (DCB) in recent trials suggests that femoral arteries are more forgiving to injury and emboli, providing more flexibility in the development of future technologies for this vascular bed. Moreover, there are some empiric observations that further point to differences in the vascular biology of different vascular beds. For example, recent studies have suggested that the migration of femoral artery vascular SMCs is more attenuated by paclitaxel than coronary vascular SMCs.[12] Nonetheless, the difficulties experienced with coronary revascularization including vessel injury, vessel closure, and ISR remain true in the peripheral vasculature. The effective durability of revascularization is directly related to patency rates, which is affected by vessel location, lesion length, occlusion versus stenosis of the artery at presentation, quality of vessel run-off, and patient comorbidities (diabetes mellitus, chronic kidney disease, and smoking).[1] Currently available treatment modalities for endovascular revascularization of the lower extremities include balloon angioplasty, atherectomy (rotational, excisional, directional, and laser), BMS (self-expanding as well as balloon-expandable stents), DES (self-expanding), and DCBs. Herein we review the concept of drug delivery via DES and DCB in peripheral arteries, being mindful of the role that the ultrastructure of the target vessel wall and its burden of disease significantly alter the vascular response to drug delivery.

PRINCIPLES OF VASCULAR DRUG DELIVERY

The advantage of DES and DCB is to provide localized delivery of a drug while limiting the risk

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