Performance of drug-coated balloons in coronary and below-the-knee arteries: Anatomical, physiological and pathological considerations

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A B S T R A C T

Below-the-knee (infrapopliteal) atherosclerotic disease, which presents as chronic limb-threatening ischemia (CLTI) in nearly 50% of patients, represents a treatment challenge when it comes to the endovascular intervention arm of management. Due to reduced tissue perfusion, patients usually experience pain at rest and atrophic changes correlated to the extent of the compromised perfusion. Unfortunately, the prognosis remains unsatisfactory with 30% of patients requiring major amputation and a mortality rate of 25% within 1 year. To date, randomized multicentre trials of endovascular intervention have shown that drug-eluting stents (DES) increase patency rate and lower target lesion revascularization rate compared to plain balloon angioplasty and bare-metal stents. The majority of these trials recruited patients with focal infrapopliteal lesions, while most patients requiring endovascular intervention have complex and diffuse atherosclerotic disease. Moreover, due to the nature of the infrapopliteal arteries, the use of long DES is limited. Following recent results of drug-coated balloons (DCBs) in the treatment of femoropopliteal and coronary arteries, it was hoped that similar effective results would be achieved in the infrapopliteal arteries. In reality, multicentre trials have failed to support the proposed hypothesis and no advantage was found in using DCBs in comparison to plain balloon angioplasty. This review aims to explore anatomical, physiological and pathological differences between lesions of the infrapopliteal and coronary arteries to explain the differences in outcome when using DCBs.

1. Introduction

Lower extremity peripheral arterial disease (LEAD) is a chronic stenotic or occlusive disease of arteries of the lower extremities that is usually a result of atherosclerosis [1]. While the prevalence of LEAD varies widely depending on the population studied, it is estimated to affect approximately 10% of adults over the age of 55 years [1]. Its overall burden, however, is more significant for women compared to men [2]; this can be explained, in part, by the fact that women usually experience an asymptomatic spectrum of LEAD thereby seeking medical treatment and intervention at a later stage than men while the severity of the disease is at its peak [3]. This is a similar trend to that of coronary artery disease (CAD) epidemiology [4]. While women often have less obstructive CAD, morbidity and mortality remain high.

Diabetes mellitus (DM) is an independent risk factor for LEAD in both men and women. A recent systematic review and meta-analysis [5] showed that DM does not confer an additional risk for LEAD in women compared to men, contradicting early results. While premenopausal women without DM are usually at lower risk of LEAD than their male counterparts, this advantage is, however, lost in the context of type 2 DM [6]. The LEAD clinical manifestations vary from asymptomatic (Stage I) to intermittent claudication (Stage II), ischemic rest pain (Stage III), and ischemic ulcer or gangrene (Stage IV) [7]. In most cases, it results from arterial stenosis due to atherosclerosis [8]; thus, it shares the same risk factors as atherosclerotic CAD. While hypertension and hypercholesterolemia are common risk factors for atherosclerosis of coronary and lower extremity arteries, smoking (with a direct positive correlation to the number of cigarettes smoked [9]), and DM (with diabetic neuropathy) are associated with more rapidly progressive disease [10]. The incidence of atherosclerosis is not just increased in diabetic patients, but its course is aggravated and accelerated; for example, the 7-year incidence of a first-time myocardial infarction (MI) is 20% in diabetic
patients compared to 3.5% in nondiabetics [11]. While the incidence of DM in patients with CAD is around 18% [12], it is about 50% in patients with LEAD [13].

While managing risk factors can address symptoms in many patients, those with quality of life limiting-claudication and those with resting leg pain or ulcer are considered for revascularisation either surgically or by endovascular intervention [14]. The ESVS 2024 clinical practice guidelines on the management of asymptomatic LEAD and intermittent claudication recommend a stepwise approach by providing risk factor management, best medical treatment, and exercise therapy as a first step, and revascularisation as a second step in compliant patients with continued disabling limb symptoms [15]. For chronic limb-threatening (CLTI) patients, revascularisation with vein bypass could be the option of choice for those of average risk suffering from severe CLTI and highly complex disease, whereas those with less intricate anatomy, medium-intensity limb threat, or heightened patient risk might be better suited for endovascular intervention [16]. All individuals diagnosed with CLTI should be provided with top-notch medical treatment, inclusive of antithrombotic, lipid-lowering, antihypertensive, and blood sugar control medications, in addition to guidance on halting smoking habits, dietary advice, and preventive foot care measures.

Endovascular treatment of LEAD involves balloon angioplasty with or without stenting. Depending on the arterial lesion characteristics, balloon angioplasty may be performed with a drug coated balloon (DCB). The surface of a DCB balloon is covered with a matrix polymer containing an antiproliferative drug to inhibit vascular smooth muscle cell proliferation and reduce neointimal hyperplasia with the aim of maintaining arterial patency [17]. A number of DCBs are currently available or are under development. The majority of balloons use either paclitaxel or a limbus-based antiproliferative agent. Paclitaxel-coated balloons (PCBs) remain the most widely used in LEAD patients with a variety of paclitaxel doses, excipients, and coating integrities [18]. The rationale of using DCBs is to deliver effectively and homogeneously an antiproliferative drug from an inflated balloon over the atherosclerotic lesion to restore and maintain luminal patency. The advantage of DCBs is that they avoid leaving the permanent metallic scaffold synonymous with drug-eluting stents (DES) whilst still delivering an antiproliferative drug to reduce late neointimal and smooth muscle cell (SMC) proliferation [19]. Local delivery of paclitaxel has been used extensively to prevent restenosis related to percutaneous angioplasty in CAD. Current recommendations [20] for using DCBs in CAD are summarized below (Fig. 1).

The use of PCBs is relatively more effective (clinically and angiographically) than plain balloon angioplasty in treating coronary in-stent restenosis (ISR); which occurs in approximately 10% of patients receiving DES, and 30% in patients receiving bare-metal stents (BMS), than in treating de-novo coronary artery lesions [21]. While DES reduces the need for target lesion revascularization (TLR) at 3 years, the incidence of composite all-cause mortality, myocardial infarction and target lesion thrombosis is similar between DES and PCB in treating coronary ISR [22]. A recent meta-analysis has raised concerns regarding the safety of using paclitaxel devices for femoropopliteal peripheral arterial disease (PAD) [23]. The study revealed a higher mortality rate with paclitaxel-coated balloons and stents in the femoropopliteal arteries, as opposed to conventional plain balloon angioplasty (all-cause mortality rate over 5 years was 14.7% compared to 8.1%; risk ratio, 1.93; 95% CI, 1.27–2.93). However, one major limitation was the inability to accurately count for patients who dropped out of the follow-up. Additionally, information on the cause of death was not available for most of the studies included in the analysis. The Food and Drug Administration (FDA) has urged gathering long-term safety data, including mortality rates, in order to form a definitive conclusion. As a result, various publications have provided conflicting results by utilizing individual patient-level data and different types of adjusted comparisons [24,25]. Nevertheless, relying on data from a single industry-sponsored study with a limited follow-up period has its limitations.

A nationwide US study was conducted at multiple centres, involving 16,560 patients who underwent femoropopliteal artery revascularization [26]. The study followed these patients for a median duration of 389 days (IQR 277–508 days). The findings revealed that among the various treatments administered, patients treated with paclitaxel-coated devices had a lower mortality from all causes within 600 days post-procedure compared to those treated with devices not coated with paclitaxel. Additionally, a retrospective analysis of health insurance claims of patients with chronic limb threatening ischaemia (CLTI), from BARMER, Germany’s second-largest insurance fund, showed that over a five-year period, the use of paclitaxel-coated devices was associated with better overall survival rates, amputation-free survival, and avoidance of major cardiovascular events when compared to non-paclitaxel-coated devices (HR 0.83; 95% CI 0.77–0.90 for overall survival; HR 0.85; 95% CI 0.78–0.91 for amputation-free survival; HR 0.82; 95% CI 0.77–0.89 for avoidance of major cardiovascular events) [27]. The study had limitations such as potential influence of the medical centre’s experience on patient survival rates, as increased continuity of care is associated with lower mortality rates [28,29]. The study, being retrospective, couldn’t gather precise data on specific devices or paclitaxel doses used in treatments. The small percentage of non-paclitaxel coatings also affected data specificity.

A recent South Korean study compared the use of paclitaxel-coated devices versus non-paclitaxel-coated devices in patients with PAD; with 6090 patients per group. The median follow-up days was 580 days (IQR 240–991 days) and 433 days (IQR 175–757 days) for the non-paclitaxel-coated device group and paclitaxel-coated device group, respectively [30]. The study demonstrated no significant difference in all-cause mortality between the two groups, despite differences in comorbidities such as diabetes and hypertension (higher in paclitaxel group). This suggests that the use of paclitaxel-coated devices did not impact the mortality of patients with PAD. However, the study did show that the use of paclitaxel-coated devices was associated with a higher rate of lower extremity amputation. The reason for this is believed to be due to the fact that during endovascular procedures, a large percentage of the paclitaxel does not reach the intended target site and is instead lost in the systemic circulation. This could lead to downstream embolization of paclitaxel particles, which could then occlude small vessels and inhibit angiogenesis at locations distant from the target site. While
this hypothesis provides a potential explanation for the higher amputation rate, further investigation is needed to fully understand the biological mechanisms at play. In a randomized trial involving patients with PAD, the use of paclitaxel-coated or uncoated endovascular devices did not result in a significant difference in the mortality [31]. The study conducted an unplanned interim analysis of all-cause mortality over a period of 1 to 4 years of follow-up. This suggests that the choice between using paclitaxel-coated or uncoated devices does not impact patient survival rates.

Even though the amount of paclitaxel administered by paclitaxel-coated devices; balloons and stents; is comparatively small to what is used in cancer treatment, concerns exist that the prolonged half-life of the paclitaxel coating, almost 2 months, could induce harmful outcomes and possibly result in embolization beyond the treated lesion [32]. It is important to acknowledge that earlier studies were not intended to evaluate long-term safety, which might have resulted in an imbalance in reporting death rates.

The safety and clinical outcome concerns with paclitaxel-coated devices for patients with chronic limb-threatening ischemia (CLTI) and below-the-knee PAD have been diluted in a recent meta-analysis of 13 studies with one-year follow-up [33]. It demonstrated that major adverse events, all-cause mortality, major amputation, and target lesion revascularization had no statistically significant difference between the PCBs group and the control group (plain balloon angioplasty). However, outcome measures beyond one-year follow-up were not feasible.

In conclusion, the safety of using paclitaxel-coated devices for femoropopliteal PAD remains a topic of concern due to conflicting results from various studies. While some studies suggest lower mortality rates, others raise issues regarding long-term safety and potential risks such as higher amputation rates.

We, therefore, hypothesize that mixed results from trials and observational studies of using DCBs in BTK-LEAD, as opposed to the optimal safety profile of DCBs in CAD, can be partially explained by anatomical, physiological and atherosclerotic plaque pathological differences between coronary and peripheral arteries. While one medical device is considered to treat one disease, the spectrum of the treated lesion, its characteristics and the pathological differences could alter the denouement. The outcome of using DCBs is a complex interaction between a variety of factors that relate to the lesion, device and technical characteristics (Fig. 2). Although meta-analyses analyzing the effectiveness and safety of DCBs reported the clinical and angiographic outcomes, various elements (e.g., balloon material, drug dose, excipient) of the DCBs and their interactions with the arterial wall have not been considered. (Fig. 3) illustrates the different elements impacting drug delivery into the arterial lesion; hence, its clinical and angiographic potency.

The objective of this review is to examine the anatomical and physiological differences between coronary and peripheral arteries and whether any of those factors can explain, solely or collectively, the different outcome of using DCB to treat an atherosclerotic LEAD lesion.

2. Anatomy of coronary and BTK arteries

Both coronary and BTK arteries are considered medium-sized (muscular) arteries with an outer diameter ranging from 2 to 10 mm [34]. Although coronary and BTK arteries share common characteristics of muscular arteries (Fig. 4), there are significant anatomical differences that may influence the efficacy of endovascular intervention.

2.1. Wall structure of coronary and BTK arteries

Coronary and BTK arteries are both classified as muscular arteries, they share common architecture and components. Despite these similarities, there are differences in the thickness of their individual layers and the proportion of components within these layers. The wall of all arteries is constructed of three concentric layers: innermost, middle and outermost [35]. The innermost layer (tunica intima) consists of an endothelial layer and a thin subendothelial layer of connective tissue with collagen and elastic fibres in layers alternating with smooth muscle cells (SMCs) layers. The middle layer (tunica media) consists mainly of concentric layers of helically arranged SMCs interposing elastic and reticular fibres. Vascular SMCs produce proteoglycans which contribute to structural and functional modifications [36].

In arteries with large diameters (i.e., elastic and muscular), an external elastic lamina separates the tunica media from the adventitia. The most external layer (tunica externa or adventitia) is composed mainly of connective tissue with type I collagen and elastic fibres [37]. The adventitia thickness reduces while travelling towards the peripheral arterial network. Large arteries have a vasa vasorum (vessels of the vessel) that provides nutrients and oxygen to cells in the tunica media and adventitia, while in smaller arteries the wall is thin enough to adequately supply the cells in those layers by simple diffusion from the blood within the arterial lumen [38]. The larger the artery, the more sophisticated the vasa vasorum network within its wall. In all arteries blood in the arterial lumen supplies the intimal cells [39].

The thickness of the three component layers of arteries is different in coronary and peripheral vessels. The orientation and number of smooth muscle cell layers and the connective tissue layers differ as per the arterial diameter. Hence, BTK arteries have more extensive layers of smooth muscle cells and a thicker adventitia than that of coronary arteries. 

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**Fig. 2.** Different factors impacting the outcome of DCBs.
arteries. Thus, their potentially different response to DCB therapy. It has been shown that the average coronary artery wall thickness is $1.1 \pm 0.2$ mm, with a luminal diameter of $2.2 \pm 0.6$ mm [40]. The diameter of the anterior tibial artery is $3.5 \pm 1.1$ mm, and that of the posterior tibial artery is $4.1 \pm 0.9$ mm [41]. The intima and media thickness increases with age [42]. However, the pattern of increase is nonreciprocal in different muscular arteries. The media thickness (MT) is reduced in a positive correlation to the distance from the heart; it has been shown that the MT of the radial artery is higher than that of the anterior tibial artery ($0.192 \pm 0.047$ and $0.178 \pm 0.049$ mm; respectively). In contrast,
the intima thickness (IT) of the anterior tibial artery is larger than that of the radial artery (0.074 ± 0.030 and 0.064 ± 0.019 mm; respectively) [42], while in coronary arteries, the IT, measured by histology, ranges from 0.10 to 0.89 mm (mean 0.29 mm) [43]. The coronary and BTK arterial walls' thickness varies around their circumference due to vascular remodelling initiated by the atherosclerotic lesion [44]. It has been shown that inflammation, calcification and thinner tunica media are primary determinants of positive remodelling that are characteristics of plaque instability [45]. While the outcome of using PCB depends partially on intima (where the absorption of the paclitaxel occurs), the difference in IT and its relation to arterial diameter could influence the target lesion revascularisation rate, and mortality associated with paclitaxel absorbed dose [46].

2.2. Microstructure of normal coronary and below-the-knee arteries

The intima of both coronary and BTK arteries consists of an endothelium and a delicate basement membrane composed predominantly of type IV collagen [47]. The intima of coronary arteries consists of endothelial cells, collagen bundles and basal lamina [48], with longitudinally arranged SMCs in the subendothelial space and more SMCs towards the intima-media junction. The intima of coronary arteries continues to grow throughout life [49,50]. The tunica media is the main determinant of an artery's elastic properties, arterial stiffness, and recoil. This layer, therefore, is important in maintaining diastolic perfusion pressure. Conversely, regardless of its thickness, the intima has no significant role in maintaining arterial pressure [51]. It is worth noting that the connective tissue thickness of the arterial wall is positively correlated to the arterial diameter and with a larger coronary diameter, a thicker connective tissue layer characterizes its structure [52]. The relative thickness of tunica intima, media, and adventitia to the entire wall thickness of both coronary and BTK arteries is shown in (Fig. 5).

The ratio of the thickness of adventitia, media, intima, and the total wall thickness of non-atherosclerotic human coronary arteries has been reported to be 0.4 ± 0.03, 0.36 ± 0.03 and 0.27 ± 0.02, respectively [53]. The adventitia of coronary arteries has dense collagen and elastic fibres that protect it from being overstretched or compressed by the contracting cardiac muscle. The adventitia is also rich in fibroblast and hydrophilic macromolecules, including glycoproteins, glycosaminoglycans and proteoglycans [54]. Combined two-photon-excited fluorescence (TPEF) microscopy and second harmonic generation (SHG) microscopy have shown that the adventitia of coronary arteries is rich in collagen bundles with much fewer elastin fibres oriented parallel to the longitudinal axis of the artery [48]. While in the outer adventitia, the collagen fibres become denser and more randomly distributed with absent elastin fibres. The collagen-to-elastin (C/E) ratio in the adventitia varies throughout the coronary tree. For example, the C/E ratio in the left anterior descending artery (LAD) is 1.5 whereas in the right coronary artery (RCA) it is 1.1 [55]. One possible explanation for this difference is the variation in diameters and the number of side branches that each artery possesses. It has been shown that the tunica media thickness (TMT) and C/E ratio rise significantly with increased blood flow [56]. As TMT has a vital role in maintaining blood pressure and perfusion pressure during diastole, via SMCs contraction, an increase in the thickness of intima and media of the carotid artery, measured by ultrasound, is positively correlated to an increased risk of myocardial infarction and stroke in individuals without cardiovascular risk [57].

The coronary artery's media layer is critical to maintain patency of the artery during cardiac contraction. It consists of concentric smooth muscle cell layers, elastic lamellae (EL), collagen, and elastin fibres. The EL are thick sheets of widely spaced elastin fibres with pores at intervals, with SMCs filling the space between the lamellae content of the dense elastin and collagen bundles interspersing the two components (Fig. 2) [58]. The tunica media has a higher C/E ratio than the adventitia, with the C/E ratio in the RCA media of 3.7 [55]. While collagen fibres show circumferential orientation, elastin presents a complex 3D structure including the layered EL, randomly distributed IL fibris and thick radial fibres [54].

Proteoglycan, secreted by SMCs, plays a significant role in their proliferation [59]. It has been shown that chronic high blood pressure (BP) increases tensile and tension stress to which SMCs respond by proliferation to induce intimal hyperplasia [60]. This relationship between high systolic BP and intimal hyperplasia can partly explain the observation that in patients with CAD, a rise of systolic/diastolic BP by 20/10 mmHg increases the risk of stroke [61], while only an increase in systolic BP is significantly associated with an increased risk of MI.

2.3. Endothelial layer of coronary and BTK arteries

The endothelial layer is composed of specialized vascular endothelial cells; squamous, polygonal and elongated cells [62]. The longitudinal axis of the endothelial cells is parallel to the direction of blood flow. Healthy endothelium has an integral role in local immune response and inflammation [63]. The endothelial cells act as a semipermeable barrier between interstitial fluid and blood to facilitate bidirectional metabolite exchange. Endothelial cells use different mechanisms to maintain adequate metabolite exchange; these mechanisms include simple and active diffusion, transcytosis and receptor-mediated endocytosis [64]. Normal endothelial function in the femoral artery is positively correlated with that of coronary arteries evidenced by femoral and coronary vascular resistance (mean arterial pressure (mmHg)/femoral average peak velocity (cm/s), and mean arterial pressure (mmHg)/coronary blood flow (mL/min); respectively) [65]. Thus, endothelial function changes in peripheral arteries reflect endothelium-dependent coronary epicardial function and coronary flow reserve [66]. Endothelial cells play a pivotal role in preventing blood clot formation by secreting antithrombotic agents (e.g. heparin, tissue plasminogen activator and von Willebrand factor) [66]. Moreover, they regulate blood flow via vascular tone control by secretion of endothelin 1, and angiotensin-converting enzyme (ACE). Both endothelin-1 and ACE (via the

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Fig. 5. The relative thickness of tunica intima, media and adventitia to the entire wall thickness in coronary and BTK arteries. (BTK; below the knee, SMCs; smooth muscle cells).
production of angiotensin II) stimulate SMCs contraction. Conversely, endothelial cells also secrete nitric oxide (NO) the principle relaxant of SMCs [67]. It has been also shown that ACE secretion from SMCs contributes to hypercholerolemia-induced atherosclerosis, independent of the circulating ACE level or blood pressure [68]. Endothelial cells also secrete various growth factors, including vascular endothelial growth factor (VEGF), and angiopoietins that stimulate endothelial cells to recruit SMCs and fibroblasts that contribute to the vascular response to injury. The role of VEGF as an angiogenesis and arteriogenesis factor has been investigated in coronary and peripheral arteries [69]. In a gene transfer porcine arterial occlusion model [70] VEGF produced a significantly enhanced capillary density adjacent to the coronary arteries without increasing the angiographic score. This contrasts with the response to VEGF in the peripheral arteries where no enhancement of capillary density was observed with a significant increase in angiographic score. This demonstrates a differential response to VEGF of predominantly angiogenesis or arteriogenesis in coronary and peripheral arteries respectively [70].

The subendothelial layer contains collagen and elastic fibres between SMCs layers. Collagen fibres maintain arterial wall integrity through their unique organization controlling wall tension and, hence, arterial wall strength [49]. Elastic fibres provide vascular wall resilience, allowing the artery to expand under pressure [37]. Elastin is a major component of the arterial wall of elastic arteries (e.g., aorta) where it forms parallel layers regularly distributed between SMCs layers. The extracellular matrix components; proteoglycans and hyaluronate; contribute to the artery's metabolic and physical properties [71]. They are responsible for arterial permeability and facilitate mechanosensing. Proteoglycan facilitates the connection between the elastic laminae and the SMCs in the arterial wall's tunica media [72].

2.4. Diameter variability of epicardial coronary arteries

The intra-population difference in the diameter of coronary arteries has been well studied [73]. These studies were motivated by a recognition that non-Caucasians have a higher incidence of CAD [74], with an earlier age at presentation. Around 25% of all myocardial infarction cases in non-Caucasians occur in those under the age of 40 years [75]. This can be partially explained by a lower mean coronary artery diameter in Asians compared to their Caucasian counterparts. The mean diameter of the left main (LM) coronary artery, left anterior descending (LAD) artery, left circumflex (LCX) artery and right coronary artery (RCA) were reported to be 2.96 mm, 2.48 mm, 2.52 mm and 2.71 mm in Asian population compared to 4.04 mm, 3.24 mm, 3.06 mm, 3.65 mm in the Caucasian population; respectively [76]. This significant reduction in mean coronary artery diameter in the Asian population renders further challenges in managing their CAD. Moreover, this discrepancy in the coronary arteries’ diameter alters the percutaneous coronary intervention outcome [77].

2.5. Diameter variability of the BTK arteries

Age plays a pivotal role in determining lower limb arterial diameter; it is positively correlated with diameter in the above-the-knee arteries including the common femoral artery (CFA) and popliteal artery (PA). In contrast, it is negatively correlated in the below-the-knee arteries including the posterior tibial artery (PTA) and dorsalis pedis artery (DPA) [78]. This age-related pattern has been reported in normotensive as well as hypertensive individuals. In hypertensive patients, the proximal arterial dilatation negatively influences the distal arteries’ diameter [79]. This effect could explain the different outcomes of using DCBs from the above-the-knee arteries to the below-the-knee ones, with the latter tending to have a smaller diameter following an intervention (either surgery or endovascular) of the proximal artery. The tendency to have a small diameter of the below-the-knee arteries could negatively impact the long-term outcome of plain balloon angioplasty and DCBs use.

Arterial diameter is also influenced by laterality. The diameter of the common femoral artery (CFA) and popliteal artery (PA) is larger on the left side, reflecting the leg's functional dominance to stabilize the body in right-handed people with a relatively larger left leg mean muscular mass [80,81]. In a healthy individual, the left CFA diameter is larger than the right CFA by an average of 0.51 mm (6% to 8%), while in distal arteries such as PTA and DPA, it is around a 20% difference. This suggests that in distal arteries, a threshold of 20% diameter difference between the right and left can delineate abnormality [78]. While the lower limb arterial diameter varies as per age and body weight, there is no difference between men and women in lower limb arterial diameter, except for DPA, when the body weight and age are considered. Furthermore, the DPA is significantly smaller in women than in men of the same age, height and body weight [78].

3. Physiology of coronary circulation and BTK blood flow

The distribution of cardiac output to the coronary and lower limb circulations involves a complex interplay of physiological factors. Understanding the regulatory mechanisms and dynamics of blood flow distribution is essential for comprehensively assessing normal function and its impact on endovascular treatment outcome.

The arterial blood pressure serves as the driving force for the blood flow in coronary and peripheral circulations. The relative distribution of blood flow is regulated by the vascular resistance within the vascular network of the perfused organ. The blood flow in cardiac and skeletal muscles differs significantly at rest and during exercise (Table 1).

Most myocardial blood flow occurs during diastole. In systole, blood flow is reduced to a great extent in the subendocardium, where the myocardium's contractile force is maximum, making it the most susceptible region for myocardial ischaemia. In contrast, most of the blood flow to skeletal muscles occurs in systole. The mechanisms involved in the local regulation of blood flow of cardiac and skeletal muscles include factors originating from within the blood vessels (e.g., endothelial-derived vasoactive factors), or factors from the surrounding tissues (Fig. 6). Whether one mechanism is predominant in one arterial territory; coronary or peripheral, the extent to which each element contributes to blood flow within each artery is still to be determined. Aside from being a potent arterial vasodilator, nitric oxide (NO) promotes endothelial regeneration and inhibits leukocyte chemotaxis [82]. It has been shown that patients with atherosclerotic CAD and LEAD have reduced NO bioavailability [83]. Moreover, patients with a genetic mutation in endothelial nitric oxide synthase (eNOS) have a higher mortality rate and in-stent restenosis following percutaneous coronary intervention [84].

3.1. Coronary and peripheral circulations in relation to the cardiac cycle

Blood flow through coronary arteries occurs mostly during diastole, in contrast to BTK arteries where most arterial blood flow happens in systole. For a typical heart rate of 75 bpm, the complete cardiac cycle takes 0.8 s, 0.3 s for systole and 0.5 s for diastole [85]. While the velocity of coronary blood flow, at rest, in angiographically normal coronary arteries during diastole is 41 ± 23 cm/s, it is 18 ± 14 cm/s in systole [86]. The absolute blood flow through an artery is determined by the product of blood velocity and cross-sectional area at the point of interest [Flow rate (Q) = Velocity of the fluid (V) X Cross-sectional area (A)] [87]. Cross-sectional area is proportional to the square of the diameter. In reality, blood flow remains relatively constant with a diameter reduction of <70–90%; as the proportion of the blood flow resistance due to the artery stenosis is relatively small in relation to the total vascular resistance of the vascular bed supplied by the artery. However, with greater arterial diameter reduction, the stenosis resistance becomes significant compared to the total resistance and; hence, the stenosis becomes “hemodynamically significant” [88]. Considerable variations
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Table 1
Blood flow in cardiac and skeletal muscles.

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<th>Heart</th>
<th>Skeletal muscle</th>
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<tr>
<td>Body weight (%)</td>
<td>0.5</td>
<td>40</td>
</tr>
<tr>
<td>Cardiac output at rest (%)</td>
<td>5</td>
<td>18</td>
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<tr>
<td>Normal blood flow (ml/min/100g)</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>Maximal blood flow (ml/min/100g)</td>
<td>400</td>
<td>60</td>
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Fig. 6. Vasoactive factors regulating blood flow. (NO) nitric oxide; (NOS) nitric oxide synthase; (L-arg) L-arginine; (EDHF) endothelial-derived hyperpolarizing factor; (PGL2) prostacyclin; (ET-1) Endothelin-1; (ECE) Endothelin-converting enzyme; (AA) arachidonic acid; (–) inhibit smooth muscle contraction; (+) stimulate smooth muscle contraction.

in coronary arteries’ hemodynamics have been reported concerning the coronary artery geometry and the flow conditions through the stenotic area [89].

The mean systolic blood pressure in the tibial arteries in a healthy individual is lower than the coronary arteries, while the diastolic pressure is higher [90]. The tibial arteries’ systolic and diastolic BPs are 142.4 ± 6.8 mmHg and 84 ± 4.4 mmHg, respectively, while coronary perfusion pressure is between 60 and 180 mmHg [91]. If, however, autoregulation of coronary perfusion falls below or above these limits, coronary blood flow decreases or increases in a linear fashion that mirrors aortic pressure [92]. When coronary perfusion pressure falls below 40–50 mmHg, the so-called pressure at zero flow indicates cessation of diastolic blood flow, hence, the coronary flow [93]. Similarly, a toe pressure < 50 mmHg indicates CLTI, whereas ischemic foot pain is suggested by a toe pressure < 30 mmHg [94].

3.2. Gap junction in coronary and peripheral arteries and vasomotor function

The gap junctions within and between the cellular layers of both coronary and BTK arteries are formed of one or more connexin proteins: Cx37, Cx40, Cx43, and Cx45 [95]. The smaller the arterial diameter, the more gap junctions are connecting SMCs [96]. Moreover, the number of gap junctions parallel the vasoconstriction and vasodilation proprieties of the artery to regulate blood pressure tissue perfusion [96]. The pattern of atherosclerosis has been shown to alter the pattern of vascular connexins; hence, the gap junction communication and vasodilatation and vasoconstriction properties of the diseased artery [97]. Similarly, blood flow disturbance and SMCs proliferation alter connexin patterns and, consequently, may influence the outcome of endovascular treatment of CAD and LEAD. Conversely, in patients with chronic lower limb ischemia with reduced BTK arterial diameter, the abundant gap
It has been demonstrated that arterial calcification represents a barrier to the optimal drug absorption of DCBs in LEAD [105]. The circumferential distribution of calcification represents the most limiting factor determining the extent of drug absorption [106]. This is in contrast to coronary calcification, where the effect of DCBs can be diluted [107]. However, in CAD, the clinical outcome of DCBs is not different between calcified and non-calcified lesions [107]. The different outcomes of using DCBs in calcified coronary and peripheral arteries can be explained, in part, by the fact that peripheral arterial calcification is most commonly associated with diabetes [108], while patients present late with intermittent claudication or CLI. Therefore, the extent of arterial narrowing and degree of arterial calcification in BTK-LEAD is greater than that of CAD where patients are symptomatic earlier [109].

In CAD, DCBs are commonly used to treat in-stent restenosis (ISR) with more encouraging data emerging to support their use in de novo CAD [106]. Moreover, the use of PCBs in non-left main coronary artery bifurcation lesions has demonstrated better clinical and angiographic outcomes (reduced target lesion stenosis) at 9 months compared with standard balloon angioplasty [107]. While DCBs are used in medium- and minimally calcified lesions in femoropopliteal arteries, DESs are used in more lengthy calcified lesions [108]. The use of DCBs in BTK arteries is considered mainly for lengthy lesions [109].

One fundamental difference in treating CAD and BTK-LEAD is the lesion’s length, as the diameter is relatively similar. It has been shown that patients with short coronary lesions (<13.4 mm), and lesions in coronary arteries with larger diameter (>2.65 mm) experience fewer major adverse cardiac events (MACE) at 2 years after treatment with either everolimus-eluting stent (EES) or paclitaxel-eluting stent (PES) compared to those with longer lesions and smaller diameter [88]. Similarly, for the BTK arterial lesions, patients with lesion length > 3 cm have a relative risk of potency loss of 2.0 compared to those with lesions ≤3 cm [89]. With longer BTK arterial lesions, blood flow resistance is expected to be higher than relatively shorter coronary arteries’ lesions, assuming similar blood vessel lengths; hence the lesion’s length is directly proportional to the arterial resistance. Whether the difference in blood flow resistance of BTK lesions and that of coronary lesions represents a valid factor explaining the outcome difference with DCBs, where the drug distribution to the endothelium depends mainly on the local blood flow’s integrity, is still to be elucidated.

5. Discussion

DCBs were developed to offer the benefits of plain balloon angioplasty with additional delivery of an antiproliferative drug to inhibit the formation of neointimal hyperplasia and reduce restenosis, maintaining arterial patency. DCBs have gained popularity to treat lesions where there is a high likelihood of restenosis or stenting is technically challenging. For example, small-diameter arteries, long lesions in peripheral arteries, arterial lesions where stent fracture is common (e.g., adductor canal), and vessel bifurcations. There is persuasive evidence that DCBs are superior to plain balloon angioplasty in treating coronary BMS/DES ISR [110,111] (class I, level of evidence A recommendation in the European guidelines for revascularization) [112]. While the use and safety of DCBs in BTK arteries are still to be elucidated, DCBs are highly recommended in femoropopliteal TASC II A and B de novo and restenotic lesions [113].

The decision to use a DCB to treat either a de-novo lesion or ISR depends on many factors including lesion characteristics such as vessel diameter, percentage stenosis, calcification, anatomical location, lesion length, thrombus burden etc. It also depends on the available DCB and the ability to deliver either balloons or stents to the lesion. Within this complexity, the different artery size and structure together with the differences in disease pattern between coronary and peripheral arteries may explain variation in the use of DCBs in these territories and the different reported outcomes. For example, while coronary lesions are often focal with intimal calcification, BTK lesions are usually long with

junctons can play a role in maintaining artery constriction after balloon angioplasty. This theoretical explanation requires further experimental investigation.

3.3. No-reflow phenomenon after endovascular percutaneous intervention

Following percutaneous coronary intervention (PCI), reduced perfusion in the absence of angiographic evidence of arterial stenosis is defined as a “no-reflow phenomenon” [98]. The mechanism of ‘no reflow’ is not fully understood. In acute coronary syndrome patients, it may relate to distal embolization of plaque or thrombus. It may also be caused by release of vasoactive substances from atherosclerotic plaque or thrombus causing microvascular vasoconstriction. The phenomenon is more common in patients who have a delayed presentation with acute ST-elevation myocardial infarction (STEMI) [99,100]. Moreover, in STEMI settings the no-reflow phenomenon was found to be a strong predictor of 5-year mortality after PCI; independent of the infarction size [105].

4. Pathology of arterial calcification and lesion characteristics in CAD and BTK-LEAD

Although atherosclerosis is a systemic disease, the pathological features of the plaques in different vascular beds are heterogeneous. Large muscular arteries lose their compliance with age, even with absent atherosclerosis and cardiovascular risk factors [72]. Different muscular arteries (e.g., coronary and BTK arteries) respond differently to age, mostly with a difference in elastin-collagen ratio and the thickness of tunica media and SMCs. The relationship between age and arterial stiffness is positively prominent in proximal arteries that are rich in elastic fibres [73]. However, it is important to note that there is a progressive increase in collagen to elastin ratio in smaller arteries further from the heart [70]. With age, elastin undergoes fragmentation, either due to mechanical or enzymatic degradation, leading to ectasia with gradual transfer of mechanical force to collagen, which is 100–1000 times stiffer than elastin [70]. Furthermore, both elastin and, to a greater extent, collagen fibres become more rigid with age due to calcification and formation of cross-links from advanced glycation endproducts (AGEs). This is more evident in diabetes mellitus [74]. While the diameter of the superficial femoral artery (SFA) is not affected by age, that of the popliteal artery (PA) increases in diameter and decreases in distensibility with age [70].

While coronary artery calcium (CAC) detected by coronary CT scan is positively and independently associated with CAD, its density is inversely associated with CAD and cardiovascular risk [110]. Moreover, coronary artery calcification with a high Agatston score of one site of coronary arteries with larger diameter (>2.65 mm) experience fewer

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medial calcification. Moreover, the nature of coronary and peripheral circulation could contribute to such difference; while perfusion pressure is similar, coronary perfusion occurs in diastole during cardiac cycle in contrast to peripheral circulation perfusion that happens in systole. Furthermore, the characteristics of the DCBs can play a significant part in such a difference. For the DCBs to confer their action, four elements interact together to achieve the desired effective drug delivery while avoiding systemic absorption: (1) coating, (2) drug dissolution, (3) drug absorption, and (4) drug distribution. While the first and second generations of DCBs used paclitaxel as an antiproliferative drug, the third generation moves into the use of sirolimus and derivatives that are less cytotoxic than paclitaxel. Therefore, it will be of interest to examine the use of sirolimus-coated balloons in the BTK arteries and investigate arterial patency and overall safety while adjusting for lesion-related factors. Concomitant with the use of sirolimus-coated balloons, a new nano-encapsulation microcrystalline coating is being used instead of the crystalline and non-crystalline coating with the first- and second-generation PCBs [114].

Alongside the lesion-related and device-related characteristics, technical factors can contribute to the outcome of DCB use. While it is recommended to inflate the DCB for 2 min, it is very operator-dependent with a range of 30s to 3 min [115], and in most published studies, the inflation time was not included in the analysis. It is, therefore, obvious that many factors contribute to the outcome of using DBCs to treat de-novo and ISR arterial lesions in coronary and BTK arteries. As in many published reports, adjusting for variable factors was not carried out; hence, any conclusion drawn from those studies only applies to the patients-set and to the centre where it was carried out. Therefore, different meta-analyses failed to reach a uniform consensus regarding the safety and the outcome of using DCBs in the BTK arteries. Whereas this review outlined the anatomical, physiological and pathological differences between coronary and BTK-lesions that could directly impact the outcome of using DCBs, examining factors related to DCBs as a medical device is warranted.

6. Conclusion

DCBs have shown a promising clinical outcome in treating coronary ISR after implantation of BMS and DES, while their successful use in treating femoropopliteal arterial lesions has been proven. However, their use and utility in BTK arteries are still to be extended. While most studies report clinical and angiographic outcomes, the complexity of interaction between anatomical- and lesion-related characteristics and the device (DCBs) features (different antiproliferative drugs, drug doses, excipients etc.) prohibits any concrete conclusion on the practicality of DCBs in BTK arteries. This review outlines the anatomical, physiological and pathological similarities and differences between coronary and BTK arteries and their lesions that could contribute to the observed clinical effectiveness and safety of using DCBs in treating arterial lesions of the two territories.

CRediT authorship contribution statement


Data statement

This is a review article with no new data created, and all data underlyng this study is cited in the references.

Declaration of competing interest

We hereby state that this review manuscript has not been previously published and is not under consideration for publication elsewhere at the moment. We are unaware of any conflicts of interest related to this publication, and there has been no substantial financial support for this work that could have impacted its results. As the Corresponding Author, I affirm that all named authors have read and approved the manuscript.

Data availability

No data was used for the research described in the article.

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