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EDITORIAL

Coronary Artery Aneurysms After Drug-Coated Balloon Angioplasty

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Drug-coated balloons (DCBs) deliver an antiproliferative agent directly to the vessel wall during balloon inflation without leaving a permanent metallic scaffold. This "leave-nothing-behind" approach preserves native vascular anatomy and function while reducing the long-term complications associated with permanent implants. DCB therapy was initially used to treat in-stent restenosis, later expanded to small-vessel and bifurcation lesions, and subsequently applied to *de novo* lesions in larger coronary vessels.[1] Although DCB angioplasty is generally considered safe, coronary aneurysm have occasionally been reported as a rare but potentially important complication. In this paper, we briefly discuss the potential mechanisms underlying coronary aneurysm formation following DCB treatment.

The available evidence on post-DCB aneurysms is derived primarily from case reports, case series, and observational studies, with reported frequencies varying widely (Figure 1). One non-chronic total occlusion (CTO) series reported no aneurysms,[2] whereas another reported an incidence of 0.8%.[3] In contrast, a CTO series reported a substantially higher incidence of 8%.[4] However, because most coronary aneurysms are asymptomatic, their detection depends on planned or clinically indicated follow-up imaging, which is not performed routinely in most patients. Aneurysms may develop relatively early after treatment, although the optimal timing of follow-up imaging remains unknown. In clinical trials, aneurysm formation is rarely defined as a prespecified endpoint, and its low incidence leaves most studies underpowered to detect differences between treatment groups. Moreover, complex lesion subsets are often excluded from clinical trials, further limiting the assessment of patients who may be at greater risk. The available literature is also susceptible to publication bias, selection bias, and surveillance bias, because patients with complex lesions, including CTOs, are more likely to undergo repeat angiography or additional imaging. Furthermore, angiographic findings suggestive of aneurysms may occasionally require intracoronary imaging for confirmation. Some areas of abnormal dilation following DCB angioplasty may represent plaque cavities rather than true aneurysms. One proposed explanation is that plaque regression leaves a cavity within the plaque while preserving the normal architecture of the vessel wall.[2] For these reasons, the true incidence of DCB-related coronary aneurysms remains uncertain and cannot be reliably estimated from the current literature.

Several mechanisms may explain why these aneurysms occur after DCB treatment. First, aneurysm formation may be related to the drug. Two

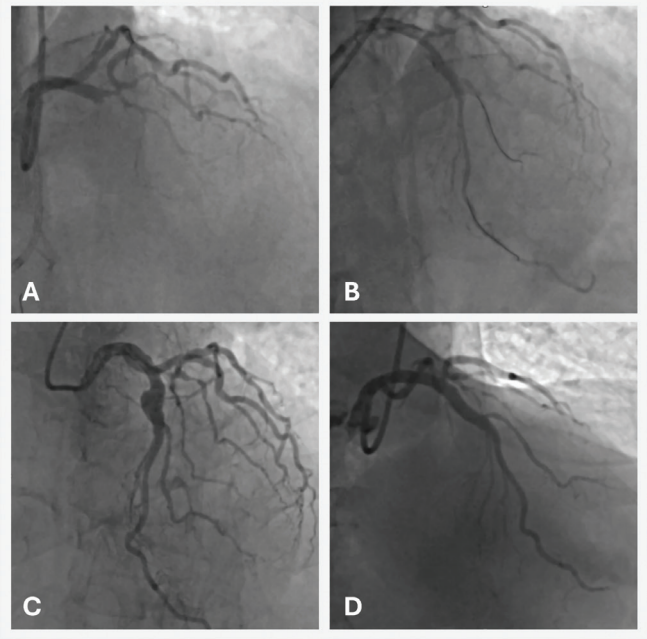

Figure 1. Coronary aneurysm after drug-coated balloons (DCB) treatment of a left anterior descending artery (LAD) chronic total occlusion (CTO). The patient was referred for percutaneous intervention of an LAD CTO (A). The lesion was crossed using antegrade wiring and treated with a DCB. Note the non-flow-limiting dissection at the proximal cap site (B). Follow-up angiography demonstrated aneurysmal dilatation of the treated segment (C). Final angiographic result after implantation of a covered stent (D)

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main classes of antiproliferative agents are used in DCBs. Paclitaxel has long been the predominant agent because its high lipophilicity facilitates rapid arterial uptake and prolonged tissue retention after brief balloon inflation. It is a cytotoxic agent that stabilizes microtubules, arrests the cell cycle in the G2/M phase, and promotes apoptosis of vascular smooth muscle cells.[5] Sirolimus, in contrast, is a cytostatic agent that inhibits the mammalian target of rapamycin pathway and induces cell-cycle arrest in the G1 phase.[5] Its lower lipophilicity and shorter tissue retention initially made balloon-based delivery more challenging. However, advances in carrier and drug-reservoir technologies have enabled the development of sirolimus-coated balloons. Although both agents inhibit neointimal growth, differences in their mechanisms of action and tissue distribution may result in distinct vessel wall responses. Experimental studies suggest that high local concentrations of paclitaxel cause greater apoptosis, smooth muscle cell loss, collagen depletion, macrophage accumulation, and disruption of the internal elastic lamina than sirolimus.[6] Moreover, paclitaxel appears to have a narrower therapeutic window, with excessive tissue concentrations potentially shifting its effects toward vascular toxicity.[6]

Late lumen enlargement (LLE), which is thought to result from vessel enlargement and plaque regression, has been described after DCB treatment of *de novo* coronary lesions.[7] LLE may occur more frequently after treatment with paclitaxel-coated balloons than with sirolimus-coated balloons.[8] However, the same cytotoxic and proapoptotic effects that contribute to positive remodeling may become excessive in some patients, resulting in medial injury, wall thinning, and aneurysm formation. Indeed, almost all published cases of DCB-related aneurysms have occurred after treatment with paclitaxel-coated balloons. This pattern, however, may partly reflect the earlier introduction and much wider use of paclitaxel-coated balloons. Moreover, coronary aneurysms have also been reported after sirolimus-eluting stent implantation.[9,10] Although the metal scaffold and polymer coating may also contribute, the role of sirolimus itself cannot be entirely excluded.

Another proposed mechanism is non-uniform drug transfer resulting from irregular plaque or vessel geometry or heterogeneous drug penetration in the presence of extensive calcification. The resulting heterogeneity in tissue drug exposure and vascular healing may create focal areas of vessel wall weakness, thereby promoting aneurysm formation.[11]

Drug dose, excipient or carrier composition, coating integrity, and tissue transfer efficiency vary among devices. Accordingly, the vascular response to DCB angioplasty may be device-specific rather than drug-specific.

A second potential mechanism is mechanical trauma. DCBs function as drug-delivery devices and are not intended for lesion modification. The lesion should therefore be adequately prepared before DCB application to achieve sufficient expansion and minimize residual stenosis and recoil. Lesion preparation using conventional non-compliant or specialty balloons, as well as advanced plaque-modification techniques such as atherectomy, inevitably results in some degree of vessel wall injury and frequently causes dissection.[12] Dissection is not necessarily an unfavorable finding. It may indicate effective lesion preparation and facilitate drug penetration into the deeper layers of the vessel wall. A higher dissection index has also been associated with more pronounced LLE,[7] potentially reflecting greater vessel wall modification and drug exposure. Concerns arise when the dissection is extensive or extends deeply into the vessel wall. When vascular healing is delayed by antiproliferative therapy, a vessel wall already weakened by medial injury may be less able to withstand intraluminal pressure in the absence of scaffold support, resulting in aneurysmal dilation. In one study, no aneurysms occurred in vessels without dissection or in those with type A dissection, and all coronary aneurysms developed at a previous dissection site, with more than half associated with type C dissections.[4] In our practice, when angiography suggests extensive dissection with deep vessel wall disruption, we have adopted a lower threshold for stent implantation.

Aneurysm formation may also depend on lesion characteristics. The risk may be greater in complex lesions because they often require more intensive lesion preparation. This is particularly relevant in CTO lesions, where vessel wall injury may result from lesion preparation as well as wire-crossing and re-entry techniques that create extraplaque tracks, medial disruption, and long dissections. The presence of

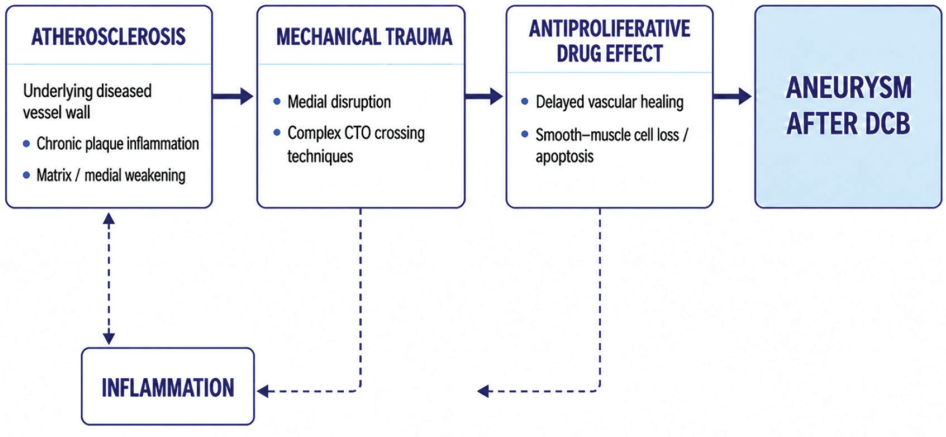

Figure 2. Possible mechanisms of aneurysm formation after DCB angioplasty
CTO: Chronic total occlusion, DCB: Drug-coated balloon

collateral circulation may also make operators more willing to accept larger dissections during CTO procedures and leave them unstented. Some of these dissections may subsequently heal through aneurysmal remodeling.

Inflammation represents a third potential mechanism. Atherosclerosis is characterized by both systemic and local inflammation. Independent of percutaneous coronary intervention, lipid accumulation, chronic inflammation, and matrix-degrading activity can weaken the media and extracellular matrix, thereby contributing to coronary aneurysm formation.[13] Mechanical trauma and the inflammatory response associated with local drug delivery may further contribute to this underlying process. This interaction may be particularly important in patients with acute coronary syndrome, in whom local and systemic inflammatory activity is more pronounced.[14,15] In this setting, the cytotoxic effects of paclitaxel may further impair vascular healing and increase susceptibility to abnormal remodeling (Figure 2).[16]

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