

Late lumen enlargement after drug-coated balloon therapy: turning foes into friends

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Assessing temporal changes in the coronary lumen provides the basis to elucidate the relative efficacy of different percutaneous coronary interventions (PCI). In this regard, angiographic late lumen loss (LLL; minimal lumen diameter [MLD] after intervention minus MLD at follow-up), as measured by quantitative coronary angiography (QCA), has been classically enthroned as the gold standard for efficacy. However, LLL depends on the acute gain (“the more you gain, the more you lose”) due to the exaggerated tissue reaction elicited by the vessel wall injury that, although attenuated, persists despite the incorporation of antiproliferative drugs. Accordingly, LLL is far from ideal for comparing the efficacy of devices with different acute gain. This typically affects comparisons of drug-eluting stents (DES) versus drug-coated balloons (DCB), where other surrogate angiographic parameters, such as MLD and % diameter stenosis at follow-up, provide more meaningful information¹. In addition, from the early studies, it was also recognised that LLL frequency distribution curves showed a unique pattern with the appearance of “negative” LLL, or late lumen enlargement (LLE), in a subset of patients. This phenomenon is of particular interest for non-stent-based technologies.

LLE after stent implantation

DES drastically inhibit neointimal proliferation but also affect the normal healing process of the vessel wall, resulting in delayed endothelialisation. Furthermore, the pharmacological properties of DES may stimulate the remodelling process, eventually leading to late acquired stent malapposition. In extreme cases, coronary aneurysms develop, and this appears to be the result of a direct toxic effect or hypersensitivity reactions elicited by the drug or the polymer². These adverse effects, which were occasionally detected with first-generation DES, are exceedingly rare with new-generation DES². In this scenario, LLE may cause acquired malapposition, increasing

the risk of stent thrombosis. With the advent of bioresorbable vascular scaffolds, the potential benefit of LLE was also studied³. LLE and positive vessel remodelling occurred with these temporal devices, particularly in small vessels³. Nevertheless, LLE may be temporally “disconnected” from the complete device resorption, resulting in late scaffold failures⁴.

LLE after DCB

DCB provide less acute gain but also less LLL than DES¹. In randomised trials, the reduced LLL and the occurrence of LLE after DCB tend to compensate for the larger acute lumen gain obtained with DES¹. Kleber et al first described the phenomenon of LLE after paclitaxel DCB angioplasty⁵. In 58 *de novo* lesions treated with DCB and undergoing angiographic surveillance at 4 months, a significant improvement in MLD (1.75 ± 0.55 mm vs 1.91 ± 0.55 mm; $p < 0.001$) was found, with two-thirds of lesions showing LLE⁵. Paclitaxel causes the inhibition of smooth muscle cell proliferation by modulating microtubule formation and upregulating proapoptotic factors. While the positive effect of apoptosis is vessel enlargement, the possible detrimental sequelae are wall thinning, aneurysm formation and rupture^{5,6}. However, these authors reviewed their series of patients treated with DCB for the occurrence of coronary artery aneurysms and found an incidence of only 0.8%, which is comparable with other interventions⁶.

As expected, LLE is more frequently detected when DCB are used in *de novo* rather than in in-stent restenosis lesions. In a small, randomised study, comparing conventional balloon angioplasty with DCB in *de novo* lesions, Funatsu et al⁷ found that angiographic LLL was significantly lower, whereas LLE was more frequently observed in the paclitaxel DCB group. Ueno et al⁸ performed serial angiographic studies at 6 months and >1 year after DCB treatment in 251 *de novo* coronary lesions. Early LLE was observed in more

than half of the lesions, but half of the lesions without early LLE eventually developed late LLE, suggesting a biphasic pattern⁸.

The pathophysiology of LLE has been further elucidated using intravascular ultrasound (IVUS), which demonstrated an enlargement of the total vessel area⁹. This finding has been related to the accumulation of paclitaxel in the adventitia, which might trigger LLE^{10,11}. Interestingly, experimental data suggest a different transverse distribution of paclitaxel and sirolimus in the vessel wall, with predominant accumulation of paclitaxel in the adventitia¹⁰. This might explain data from recent studies suggesting that LLE is more frequently seen after paclitaxel DCB therapy than after limus DCB therapy¹². Yamamoto et al suggested that the mechanism of LLE after paclitaxel DCB was twofold: growth of the entire vessel and regression of plaque volume⁹. Using serial IVUS studies, they demonstrated an increase in external elastic membrane and lumen volumes and a reduction in plaque volume, with 74% of lesions exhibiting LLE. The “dissection index” (a measure of dissection severity) emerged as the strongest predictor of LLE. These authors speculated that dissections could facilitate paclitaxel reaching the adventitia, therefore inducing LLE⁹.

Present study

In this issue of *EuroIntervention*, Yamamoto et al¹³ assessed determinants of LLE after DCB treatment in *de novo* lesions using serial optical coherence tomography (OCT) imaging. A total of 83 patients with 108 lesions, with successful paclitaxel DCB angioplasty and available OCT at follow-up (median 6.1 months), were analysed. LLE was detected in 44 (40.7%) lesions, but not all cases displaying volumetric LLE had an increase in minimal lumen area. Fibrous/fibrocalcific and layered plaques had significantly larger lumen volumes at follow-up. Lesions with a medial dissection arc >90° also showed an increase in lumen volume. Conversely, LLE did not occur in lipid plaques. On multivariate analysis, layered plaques (odds ratio [OR] 8.73, 95% confidence interval [CI]: 1.92-39.7) and medial dissection with an arc >90° (OR 4.65, 95% CI: 1.63-13.3) were independent predictors of LLE. Importantly, LLE was associated with a reduction in angiographic binary restenosis and repeat revascularisation¹³. This is a very interesting study shedding new light on the pathophysiology of LLE after DCB therapy. However, discussing some methodological issues would be of value.

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First, this is a retrospective, small, single-centre study, without an independent centralised core lab analysis, and, therefore, results should be considered as exploratory and hypothesis-generating. Likewise, only patients with available OCT images at follow-up were included. This suggests a potential selection bias. Complex lesions were also excluded, and, therefore, the generalisability of the results to unselected patients treated with DCB should be confirmed in prospective studies. Second, plaque phenotype (layered morphology) and dissection type were independently associated with LLE. Of note, OCT is by far superior to IVUS in assessing these subtle anatomical features due to its unsurpassed resolution. The significance of the type of dissection complements previous studies suggesting that non-occlusive dissections favour LLE. In a previous OCT study, Sogabe et al¹⁴

also demonstrated that deep dissections after DCB predicted the occurrence of LLE. Interestingly, reattachment and healing of the dissection flaps at follow-up were detected in patients showing LLE. A large dissection reaching the media may help to set free the vessel wall, facilitating positive remodelling, and may also favour paclitaxel reaching the adventitia. However, in the present study, most patients (91%) were predilated with scoring/cutting balloons, and this should be taken into account when interpreting the results of dissections.

Interestingly, a layered plaque morphology was also a predictor of LLE. Notably, layered plaques on OCT have recently generated great interest, as they represent the morphological surrogate of healed plaques on pathology. Importantly, layered plaques have been associated with distinct clinical, anatomical, and prognostic implications (plaque progression) in recent OCT studies¹⁵. These investigators speculated that layered plaques may be more prone to plaque regression after DCB treatment, but, unfortunately, data in this regard were not provided. The reason why layered plaques are associated with LLE remains unclear and should be addressed in further studies. Finally, despite its unique resolution, OCT has limited penetration into the vessel wall. Therefore, critical players in the LLE process, such as positive remodelling and plaque regression, could not be ascertained. Studies with a combined use of OCT and IVUS will be required to comprehensively elucidate the complex pathophysiological interplay among all these anatomical factors related to LLE.

The LLE phenomenon is emerging, together with inhibition of neointimal proliferation, as the main mechanism of DCB efficacy. Whether this unique phenomenon is just a marker of clinical efficacy or whether it might still be associated with some potential untoward long-term adverse effects warrants additional investigation.

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Conflict of interest statement

The authors have no conflicts of interest to declare in relation to this work.

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