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Relevance of Coronary Evaginations in Bioresorbable Vascular Scaffolds☆,☆☆,☆☆☆

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Bioresorbable scaffolds (BRS) for percutaneous coronary intervention (PCI) have emerged with the promise to restore physiologic pulsatility and vasomotion, promote plaque regression and stabilization, and remove the trigger for late adverse events and stent thrombosis (ST). ST is a serious complication due to the high morbidity and mortality in both the short and long term. Although the rates have been reduced in newer-generation drug-eluting stents (DES) with advances in stent design and pharmacotherapy, the risk of ST continues to persist for all DES and was even higher with current-generation BRS. Causes associated with ST include incomplete neointimal formation, underexpansion, dissections, malapposition, hypersensitivity reactions, positive remodeling, and neoatherosclerosis. Intracoronary optical coherence tomography (OCT) visualizes in detail the majority of these features and has, therefore, become the gold standard to study their natural history and clinical importance. In this endeavour, the phenomenon *coronary evagination* has been observed by OCT in DES and is proposed to be an additional risk factor of late and very late ST [1].

In the present issue of the journal, Blachutzik and colleagues retrospectively analyzed coronary evaginations visualized with OCT in 8 patients with previously implanted Absorb bioresorbable vascular scaffold (BVS) who had a clinically driven angiography showing *peri-stent contrast staining* (PSS) at the BVS site [2]. In comparison with a control group of patients without angiographic PSS, the authors report a larger lumen and scaffold area in the evagination group, which also exhibited a greater frequency of malapposed and fractured struts. Further, they found a positive correlation between the lumen and scaffold size in relation to time from implantation. The proposed mechanism for this allegedly progressive increase over time in scaffold size is that the scaffold follows, in variance to metallic DES, the outward remodeling of the artery, at least when it occurs after the loss of structural integrity. The suggested correlation between scaffold dimensions and time is indeed interesting; however, further interpretation of the results requires careful consideration of the methods together with an acquaintance with the unusual terminology of features studied in relation to coronary evaginations.

1. Assessing evaginations and related parameters

Evaginations denote an outward bulge in the luminal vessel contour between struts as seen in a 2D cross-section by OCT at follow-up after stent or scaffold implantation. They were first described in cases of very late ST in sirolimus-eluting stents (SES) but attracted interest when found in SES-treated lesions of asymptomatic patients [3,4]. In the literature, they have also been referred to as multiple inter-strut hollows, cauliflower effect, peri-stent ulcers, and extra-stent lumen [5,6]. Larger OCT-detected evaginations have been shown to correspond to contrast staining outside the stent contour by angiography, so-called PSS, which was observed in 2% of SES-treated lesions and was associated with very late ST at 3 years [6,7]. Evaginations can be characterized by depth, area, and volume; and systematic analysis has shown that OCT-detected evaginations irrespective of size are frequently found in both early- and newer-generation DES (40% to 70%). Nevertheless, when considering evaginations in three dimensions – so-called *major evaginations* – they remained common in SES (~25%) but were less frequent in paclitaxel- and biolimus-eluting stents (10% to 15%) and were rare in newer-generation zotarolimus- and everolimus-eluting stents (~3%). At the same time, major evagination volumes were significantly larger in SES than in other stent types (up to 30 mm^3 vs. ~5 mm^3), which suggests large evaginations to be a morphological footprint of SES [1].

Coronary evaginations in BVS are not new. Several cases have been reported, and in a one-year follow-up study by Gori et al., 54% of 105 analyzed BVS exhibited this feature (~2 mm^3 per scaffold), out of which

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☆☆ Blachutzik et al. Major coronary evaginations following implantation of bioresorbable vascular scaffolds – Clinical and OCT characteristics

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only one fulfilled the criteria of major evagination (minimum evagination depth 10% of scaffold diameter and >3 mm consecutive frames with evaginations), suggesting that these were generally small in that study [8]. By angiography, PSS was reported in 18% of BVS, which is surprisingly high compared to an unselected SES cohort (2%). The study by Blachutzik does not provide further information on the occurrence of PSS and evaginations in BVS because the patients with evaginations (8 of 94 [8.5%] patients exhibiting PSS) were selected by individual operators for OCT among BVS-patients referred for a clinically driven angiography. Hence, they were examined at various time points. Considering that OCT-evaginations may also be present in patients without PSS, it is surprising that none of the 20 of 86 patients without PSS had any evaginations by OCT. With BVS further being translucent by angiography (making the assessment of extra-stent contrast staining particularly difficult), it would have been interesting to know the reproducibility of this feature.

The main results of the paper in focus hover around the finding of a larger lumen and scaffold size, as well as a greater frequency of malapposed and fractured struts in lesions with vs. without evaginations. Although it is tempting to compare this with similar results from previous studies of metallic stents [1], two things are imperative to note: the first is the fact that the statistical analysis was performed without consideration of the hierarchical structure of OCT data, which, as recently highlighted, is crucial in order not to underestimate the effect of clustering [9]. Second is the rather untraditional way of normalizing the scaffold and lumen dimensions to account for the absence of baseline OCT – namely to the reference vessel size by baseline quantitative coronary angiography (QCA). Although it is suggested that the error is systematic and thus "equal" in both the evagination and control groups, this is not supported by available studies of the agreement between QCA and OCT: Mazhar et al. found a good correlation for lumen diameters between 2D-QCA and OCT [10]; Tu et al. saw an acceptable correlation in lumen areas between 3D-QCA and OCT [11]; whereas Gutierrez-Chico specifically evaluated segments with BRS, finding poor agreement between OCT and QCA by both video-densitometry and edge detection [12]. Considering the conflicting results of these studies, conducted with different methods, we can conclude that the normalization procedure used by Blachutzik et al. is unreliable, and it is unclear how to interpret the results, even though intriguing. It would have been interesting if the authors had analyzed the reference vessels by QCA at both baseline and follow-up, and by OCT at follow-up, which would have allowed an estimation of possible vessel differences in the two groups and whether these were present already at baseline or acquired with time.

2. Dynamics, mechanisms, and clinical implications of evaginations

Thus far, data on metallic stents have demonstrated an association between the presence and extent of evaginations, and malapposed and uncovered struts, as well as the co-location of evaginations with subclinical thrombus [1,13]. Serial IVUS analysis has proposed positive remodeling as a plausible underlying mechanism, possibly related to an inflammatory reaction against the SES polymer, which may induce positive remodeling through destruction of the media, leading to evaginations and, eventually, stent detachment with malapposition [1,3,13]. The further association with flow disturbances by fluid-dynamic simulations [14] altogether suggests evaginations to be an adverse feature.

As for the mechanisms of evaginations in BVS, Gori et al. recently suggested underexpansion of the BVS at implantation, which speculatively may have led to malapposition due to uncorrected underexpansion as well as strut fractures due to overexpansion of the scaffold after postdilatation [8]. Another explanation could be a negative recoil related to the loss of radial strength during resorption. In spite of the small sample size of the study by Blachutzik et al., it is interesting that lumen and scaffold sizes tended to be greater with the time from follow-up, although there was no correlation with the number and size of evaginations. It is tempting to suggest that positive remodeling could be involved in the pathogenesis of evaginations in BVS, too. Part of this mechanism could be related to the loss of radial strength during bioresorption, allowing the scaffold to "dilate" during remodeling; however, regression of plaque behind the scaffold could also be a possibility, as previously suggested [15]. In any case, as long as serial data are not available, this remains speculation.

Systematic data exist thus far only for the angiographic correlate PSS. A 5-year follow-up of the j-Cypher registry with >7.000 SES-implanted lesions that had undergone angiography at 12 months (2.5% lesions), showed a significantly higher cumulative incidence of very late ST in lesions with PSS than in those without (5.3% vs. 0.7%, $p<0.0001$) [16]. In contrast, a cohort of 1.081 lesions with everolimus-eluting stents showed no differences in clinical events at 5 years in the group with PSS at one year (3% lesions) [17]. Similarly, a substudy of the HORIZON trial randomizing patients to paclitaxel-eluting or bare-metal stents demonstrated no clinical events at 3 years in the 6 lesions that exhibited PSS at 13 months [18]. Similar data for BVS or other BRS are not available. Nevertheless, based on this and other discussed features in this editorial, it is fairly reasonable to assume that evaginations and PSS remain a footprint of first-generation SES, with clustered adverse events at long-term follow-up that seem to relate specifically to this device and with much less importance for other devices including BRS.

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