Casting light on coronary evaginations: different mechanisms in different coronary devices?

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This editorial refers to ‘Coronary evaginations and peri-scaffold aneurysms following implantation of bioresorbable scaffolds: incidence, outcome, and optical coherence tomography analysis of possible mechanisms†', by T. Gori et al., on page 2040.

Stent thrombosis (ST) remains a major concern due to high morbidity and mortality in both the short and long term. Although the rates of this complication have been reduced with newer generation drug-eluting stents (DES), the risk of ST continues to persist for all DES and was recently also reported in bioresorbable vascular scaffolds (BVS). Among the suggested causes of ST are incomplete neointimal formation, malapposition, hypersensitivity reactions, positive remodelling, and neoatherosclerosis. Intracoronary optical coherence tomography (OCT)—a near-infrared light-based technology with an ultrahigh resolution (10 μm)—visualizes in detail the majority of these features which are also seen in asymptomatic patients. OCT has therefore become the tool of choice to study their clinical importance and natural history in order to prevent future ST. In this endeavour, a new phenomenon, coronary evagination, has been observed by OCT in DES, and proposed to be an additional risk factor of late and very late ST.

In the present issue of the journal, Gori and colleagues describe, using OCT at 12 months follow-up, the incidence, predictors, and possible mechanisms of evaginations following implantation of the everolimus-eluting Absorb BVS (Abbott Vascular, USA). Out of the 102 studied lesions, 54% exhibited one or more evaginations, whereas the entity ‘major evagination’ was rare. Evaginations were strongly associated with malapposition and strut fractures, as well as with peri-strut low-intensity areas (PSLIAs), thought to represent poor scaffold healing. The proposed mechanism of evaginations in this BVS cohort was scaffold undersizing. The study is exciting as it for the first time reports coronary evaginations in the Absorb BVS, and proposes a different mechanism from that in DES. Nevertheless, interpretation of the results requires careful consideration of the methods, and a general acquaintance with the unusual terminology of features studied in relation to coronary evaginations.

What are evaginations and where can they be found?

The OCT phenomenon coronary evaginations was described in around 2010, and has in the literature also been referred to as multiple interstrut hollows, cauliflower effect, peri-stent ulcers, and extrastent lumen. In all cases, it denotes an outward bulge in the luminal vessel contour between stent struts, as seen in two-dimensional cross-sectional view by OCT at follow-up after stent implantation (Figure 1A). The interest in evaginations was triggered by the finding in cases of very late ST in sirolimus-eluting stents (SES), and fuelled by the observation of this odd vessel appearance also in asymptomatic patients with this stent. Larger OCT-detected evaginations have been shown to correspond to angiographic contrast staining ‘outside’ the stent contour, so-called peri-stent contrast staining (PSS), which although absent in bare-metal stents, has been observed in 2% of SES lesions and associated with an increased incidence of target lesion revascularization and very late ST at 3 years. Systematic analysis has shown that evaginations irrespective of size are frequently found in early-generation SES (~70%) and paclitaxel-eluting stents (PES) (~50%), but also in newer generation everolimus- (EES), zotarolimus- (ZES), and biolimus-eluting stents (BES) (~40–50%). When considering evaginations in three dimensions, major evaginations (MEs) with a depth ≥0.3 mm and length ≥3 mm remained common in SES (~25%) but were less frequent in PES (~10%) and BES (15%), and rare in ZES and EES (~3%). At the same time, ME volumes were significantly larger in SES compared with other stent types (up to 30 mm³ vs. ~5 mm³), suggesting large evaginations to be a morphological footprint of SES.

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Using a similar definition, Gori et al. observed evaginations in 54% of BVS (≏2 mm$^3$ per scaffold) with MEs present in one lesion alone. By angiography, PSS was reported in 18% of BVS, which is rather high compared with an unselected SES cohort (2%).$^{12}$ Although it is tempting to conclude that evaginations in BVS occur at a similar frequency and size as in newer generation stents, it is noteworthy that the statistical analysis was performed without the consideration of the hierarchical structure of OCT data, which, as recently highlighted, is crucial in order not to underestimate the effect of clustering.$^{13}$ This shortcoming therefore makes a direct comparison of the data by Gori et al. with that
from previous studies problematic. As for PSS, it should be noted that BVS are radiolucent by angiography, making the assessment of extra-stent contrast staining particularly difficult with the possibility of both over- and underestimation. It would therefore have been interesting to report the reproducibility of this feature.

**Is evagination an adverse feature and what is the mechanism?**

Several studies of 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. Positive remodelling as assessed by serial intravascular ultrasound (IVUS) has been proposed as the underlying mechanism, and by closer evaluation it is intriguing that evaginations/PSS and malapposed struts share common patterns in terms of: the occurrence in different stent types, as well as the correlation with histopathological signs of hypersensitivity in SES. Taken together, evaginations seem to be an adverse feature, and it may be proposed that particularly larger evaginations such as those in SES are caused by an inflammatory reaction against the polymer, inducing a positive remodelling and destruction of the media, which leads to evaginations and eventually stent detachment, causing malapposition with collapse and loss of already developed intimal tissue.

In spite of the statistical limitations of the study by Gori et al., it is interesting that the extent of malapposition and strut fractures tended to be greater in BVS with vs. without evaginations. Since a similar trend could not be detected for uncovered struts, the authors evaluated instead the signal intensity of the covering tissue as a surrogate of tissue composition. This is exciting considering that a lower signal by OCT (PSLIA) may indicate the presence of fibrin as a surrogate of tissue composition. This is exciting considering that the utility of PSLIAs in clinical studies remains to be established, it is relevant to consider some aspects that may affect the interpretability of OCT image interpretation to enable such a differentiation.

Concerning the causes of evaginations in BVS, it should be emphasized that the study of the mechanisms of features occurring at the cross-sectional level (e.g. evaginations) requires serial cross-sectional visualization of the vessel wall in both the reference and scaffolded segments. In the study by Gori et al., the only serial data available were derived from quantitative coronary angiography, which is limited by its lumenographic nature. Using these data, the authors report that reference vessel diameters were generally larger in lesions with evaginations at both baseline and follow-up; however, in-scaffold minimal lumen diameters were smaller than in the reference vessels but similar between groups, suggesting a relatively greater degree of scaffold undersizing in the evagination group. At the same time, post-dilatation was performed more often in lesions that developed evaginations. Altogether, the authors suggest that evaginations in BVS may arise from undersizing at implantation, with poor vessel healing playing a role. Although a definitive conclusion on the mechanism of evaginations in BVS is not possible, it could be speculated that the course of evaginations in BVS may involve the fact that acute undersizing may lead to both malapposition due to uncorrected underexpansion and strut fractures due to overexpansion after post-dilatation. In either case, incompletely apposed struts are known to heal at a slow pace such that, on the one hand, neointimal tissue remains signal poor and ‘immature’ for a longer time compared with well-apposed struts; and, on the other hand, during the ‘filling in’ of neointimal tissue between the malapposed/fractured struts and vessel wall, the luminal contour may take on an evagination-like corrugated appearance (Figure 1E). Accordingly, evaginations need not necessarily be caused by adverse positive remodelling, which, considering the biocompatible nature of the polylactide polymer, seems unlikely in BVS.

Finally, it should be mentioned that as compared with the described acute underexpansion, ‘acquired underexpansion’ may potentially also occur in BVS in relation to the loss in radial strength during polymer bioreosorption, or due to fatigue leading to scaffold fracture. Although polymeric scaffolds in contrast to metallic stents may be particularly prone to this, it is notable that second-generation BVS were designed specifically to circumvent this.

**Clinical implications and lessons for the future**

With prospective data on the clinical impact of evaginations pending, several findings support the notion that they are predictors of late adverse events. In BVS, the correlation with undersizing may be critical considering the association of severe underexpansion with acute ST. Further data are needed to elucidate the extent of BVS undersizing, and the potential risk with different degrees of underexpansion.

Concerning DES, evaginations and malapposition suggestively represent a continuum of the same dynamic process rather than separate entities. This is supported by data showing a progression in evagination and PSS size in SES with time, accompanied by a simultaneous increase in the rate of malapposition. Such continued positive remodelling might explain how patients with SES having MEs...
by OCT. PSS by angiography, or aneurysms by IVUS subsequently developed very late ST.12,14,26

With evaginations being relatively frequent by OCT, it may be surprising that they are only now attracting attention. This is probably related to focus previously being concentrated on other predictors of ST: uncovered and malapposed struts. With OCT allowing detailed serial evaluation of these features, it is remarkable that they have not yet been prospectively correlated with ST.5 The cause of this is not completely clear; however, a closer look at evagination they have not yet been prospectively correlated with ST.5 The cause of this is not completely clear; however, a closer look at evagination it is interesting to speculate whether we should be looking for specific risk features in specific stents rather than assessing the same variables in all devices. This is supported by histopathology showing that different DES are associated with different vascular responses which, particularly in SES, involve inflammation of the media with positive remodelling.22 In continuation of this, relevant features might create a clearer signal when considered in three dimensions (e.g. MEs) which integrates information about clustering and extent, in stead of merely at the two-dimensional cross-sectional level.5 Finally, the evaluation of a combination of features, such as co-located evaginations, and malapposed and uncovered struts, might be more useful in expressing the risk of ST rather than that of a single feature alone. While awaiting prospective clinical data in metallic and polymeric devices, these points suggest that we should already now consider adjusting current intracoronary imaging methods according to what we have learned so far. This is expected to help us to extract more information out of available high-resolution OCT data, and eventually improve our ability to predict and prevent adverse events.

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References

A rare case of ascending aortic stenosis

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A 48-year-old woman was referred to an in-hospital cardiology evaluation after performing a transthoracic echocardiography (TTE) that indicated a severe aortic valvular stenosis. She had a cognitive delay, short stature and long-term symptoms of fatigue for moderate exertion. No history of syncope or angina.

The TTE was repeated and revealed a tricuspid aortic valve with mild calcification, maintaining good opening; a left ventricular obstacle, apparently with a supra-valvular location, with a maximum velocity of 5.6 m/s and a mean gradient of 85 mmHg; left ventricular hypertrophy with good systolic function (Panels A and B). A transoesophageal echocardiogram confirmed the good opening of the aortic valve (Panel C), but the proximal ascending aorta was poorly visualized. The cardiac magnetic resonance imaging confirmed the severe supra-valvular aortic stenosis, with nearly interruption of the aortic root (Panel D).

The case was discussed by a multidisciplinary team, having reached the probable diagnosis of Williams syndrome. This disease affects the elastin gene, leading to a generalized arteriopathy with diffuse or localized stenosis of large- or medium-sized arteries. The ascending aorta above the valve and the pulmonary arteries are one of the most affected locations. The cognitive delay and the short stature are characteristics of this syndrome. The patient underwent surgical correction with Brom’s technique — symmetric aortoplasty with three patches that expand Valsalva sinus (Panel E).

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