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EDITORIAL COMMENT

The Return of Coronary Vasomotion After Bioresorbable Scaffold Implantation*

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The coronary artery endothelial lining maintains vascular tone and regulates blood flow. Mechanical forces such as increased shear stress trigger activation of endothelial cells, prompting generation of nitric oxide (NO) and prostacyclin, which promote vasodilation and increased flow. NO causes relaxation of vascular smooth muscle cells as well as inhibition of smooth muscle cell proliferation, inflammation, and thrombosis. As a counterbalance, the endothelium also produces vasoconstrictors such as endothelin-1.

When the endothelium does not function normally, pathological vasoconstriction can occur due to direct smooth muscle stimulation. An absence of functioning endothelium may lead to myocardial ischemia, thrombosis, repeated revascularization, inflammation, and atherosclerosis progression. Epicardial and microvascular coronary endothelial dysfunction independently predict worse functional capacity and acute cardiovascular events, even in the absence of obstructive coronary artery disease (1). Acetylcholine (ACh) causes release of NO and subsequent vasodilation in the presence of healthy endothelium. However, in the absence of endothelium or with dysfunctional endothelium, ACh acts directly on the smooth muscle cells causing vasoconstriction.

VASOREACTIVITY AFTER STENTING

Descriptions of persistent impaired vasoreactivity after coronary intervention first surfaced with the first-generation drug-eluting stents (DES). Bare-metal stents appear to have a neutral effect on post-stent epicardial reactivity in response to exercise or ACh (2,3). First-generation DES, however, were associated with paradoxical vasoconstriction in response to ACh or exercise for at least 6 months (3,4). Second-generation DES may not be as plagued by impaired vasomotion as first-generation DES (5). The clinical implications of impaired vasoreactivity after DES are not clear, although patients with endothelial dysfunction after DES placement may have more adverse clinical events (3).

BIORESORBABLE VASCULAR SCAFFOLD SYSTEM DEGRADATION

Potential benefits of a fully bioresorbable scaffold include restoration of vessel anatomy and physiology, greater conformability, and a reduced thrombogenic milieu. The ABSORB Bioresorbable Vascular Scaffold system (BVS) (Abbott Vascular, Irvine, California) is composed of poly-L-lactic acid and releases everolimus. The BVS undergoes a 3-stage bioresorption process, ultimately being metabolized to lactate and then CO_2 and H_2O. There is a reduction in radial support after 6 months, and the scaffold is fully resorbed by 3 years.

Comparisons between the second-generation DES and the BVS indicate comparable angiographic and clinical outcomes. However, initial clinical evaluation of the BVS suggests the return of vasomotion at 12 months, implying return of normal vessel size and pulsatility after BVS implantation. This time point corresponds to significant loss of BVS molecular weight and scaffold radial strength. Supporting this finding is the report of a lower rate of recurrent angina after BVS than Xience (Abbott Vascular) in the ABSORB II randomized controlled trial (6).

Brugaletta et al. (7) focused on vasomotion within treated segments at 12 and 24 months in patients

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from the ABSORB trials. ACh and nitroglycerin were used to test endothelium-dependent and -independent vasomotion. Healthy vasodilation with ACh was associated with greater BVS intravascular ultrasound echogenicity, along with greater resemblance of nonscaffolded vessels. Abnormal vasoconstriction with ACh was associated with greater plaque burden and necrotic core. These findings suggest that the return of healthy endothelial function depends on both degradation of the scaffold and the extent of underlying atherosclerotic disease.

Onuma et al. (8) posit that return of normal vasomotion within the scaffolded segments clinically indicates that the covering endothelial lining is confluent, the ciliary function of the endothelial cells is appropriate, and the biochemical process to release NO is working properly. Return of vascular pulsatility and lumen normalization has been assessed in a nonatherosclerotic swine model, comparing BVS and the Xience V stent. In the scaffolded arteries, at between 12 and 42 months, there is a progressive increase in the lumen areas and return of pulsatility, whereas the stented segments have unchanged lumen areas and a lack of pulsatility (9).

WHAT THIS STUDY SHOWS

The paper by Gogas et al. (10) in this issue of *JACC: Cardiovascular Interventions* focuses on vascular responses in miniswine arteries after implantation of the ABSORB scaffold or the Xience V stent at 1 and 2 years. The authors demonstrated return of vascular reactivity at the site of the BVS implant at 1 year, which remained at 2 years, and a numerically greater responsiveness in the vessel proximal and distal to the BVS than to the Xience stent. Ex vivo evaluation of the adjacent coronary arteries demonstrated vasoconstriction with prostaglandin F2α, endothelium-dependent vasodilation with substance P, and endothelium-independent vasodilation with nitroprusside in arteries implanted with the BVS but not with the Xience. Evaluation of messenger ribonucleic acid levels of endothelial and smooth muscle cell functional markers revealed only a difference of 1 marker at 2 years, with an increase in connexin 43 in the BVS group at 2 years. No differences in functional markers were found at 1 year.

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It is important to note that the scaffolded BVS segments have a return of full vasoactive response at 1 year, without further change at 2 years. These vasoactive changes within the BVS at 1 and 2 years are similar to the unscaffolded adjacent coronary segments, indicating the return of normal vascular motion. Ex vivo coronary dilation and constriction in response to vasoactive substances are also significantly greater in BVS vessels than in Xience segments.

The authors chose a nonatherosclerotic model to focus on the underlying differences in vasoreactivity response without the confounding influence of atherosclerotic changes (7). It should be noted that in the porcine model, in contrast to humans, ACh caused nonendothelium-dependent vasoconstriction due to a direct effect on medial smooth muscle cells. The authors also noted greater connexin 43 at 2 years in the BVS-treated vessels compared with DES. Intercellular communication between vascular wall cells occurs via gap junctions that are aggregates of connexin proteins. One of these connexins is connexin 43, found primarily in vascular smooth muscle cells but also in endothelial cells. Connexins play an important role in vascular physiology including influencing vasomotor tone. The level of connexin 43 expression is influenced by shear stress. It is present in atherosclerotic plaque. It is also significantly increased in stent-induced intimal thickening and in the presence of mechanical strain and fluid shear stress (11). It is not clear what the role of increased connexin 43 messenger ribonucleic acid in this study indicates because increased connexin 43 expression is increased in porcine stent-induced intimal thickening (12) and, in some settings, increases smooth muscle cell proliferation and differentiation in vitro (13). This difference in 1 smooth muscle cell marker does not provide a clear mechanism for the differences in vasomotor function, particularly because there is no difference in this marker at 1 year despite the return of normal vasoreactivity.

This paper provides evidence of return of normal vascular function in the scaffolded sections by 1 year, with return of adjacent vasomotion. It also demonstrates persistent endothelial dysfunction adjacent to second-generation drug-eluting stented segments even at 2 years despite complete endothelial coverage. These findings suggest that return of vasoreactivity may be multifactorial. After bare-metal stent placement, the adjacent vessel has preserved vasomotion. Perhaps both the presence of a permanent implant and the presence of drug release influence the return of vasoreactivity. What is exciting in this paper is the return of normal vasoreactivity, both within the scaffolded segments and the implanted artery.

Although data are not yet available for differences in patient outcomes based on changes in vasoreactivity, it is clear that abnormal vasomotion can lead to increased anginal symptoms after DES placement. Additionally, the inability to appropriately vasodilate after exercise (2) may lead to impaired functional

capacity. Endothelial dysfunction has been associated with a greater risk of cardiovascular events (1). Thus, the future is bright with the possible return of coronary arteries to a healthy functional state after intervention.

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