EDITORIAL COMMENT

Temporal Course of Neointimal Formation After Drug-Eluting Stent Placement

Is Our Understanding of Restenosis Changing?*

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Drug eluting stents (DES) were designed with the primary purpose of inhibiting neointimal formation after percutaneous coronary intervention. Early data from randomized clinical studies confirmed the efficacy of these devices in preventing restenosis when compared with bare-metal stents (BMS) 6 to 8 months after implantation (1,2). However, given that the period of drug release is relatively short (i.e., <90 days) after DES implantation in animal models and that preclinical studies done by us and others demonstrate a late “catch-up phenomenon” in terms of an increase in neointimal thickness from 1 to 3 months, an important unanswered question remains: “Do DES halt the restenotic process or merely delay it?” (3–5). Our data from human pathology from patients dying after DES placement indicate incomplete healing as long as 50 months after device placement (6).

In this issue of JACC: Cardiovascular Interventions, Byrne et al. (7) present data from an observational study of patients receiving permanent polymer rapamycin-eluting stents (RES), permanent polymer paclitaxel-eluting stents (PES), or polymer-free rapamycin-eluting stents (pf-RES) who underwent serial angiographic follow-up at 6 to 8 months (i.e., early) and 2 years (i.e., late) after stent placement. The RES and PES demonstrated significant increases in late lumen loss from early to late follow-up, whereas pf-RES showed essentially no change. These data demonstrate that the arterial response to these devices is a dynamic process lasting well beyond the 6-month time point chosen for angiographic follow-up in clinical trials and highly dependent on the type of DES (i.e., polymeric vs. nonpolymeric) as well as the duration of drug release. These factors might heavily influence the temporal course of intimal formation and healing after DES placement. This study also puts in doubt the belief that polymeric slow release of the drug is essential for long-term efficacy of DES.

Much of our current understanding of the vascular responses to DES has been generated from animal data. Given the limited resolution of conventional angiography, intravascular ultrasound, or other modalities, preclinical histological studies remain the most effective means of evaluating arterial responses to vascular stent implants and have helped lend insights into human responses (8). Although arterial repair after stent placement in normal animal arteries occurs more rapidly than in humans, the sequence of biological responses are remarkably similar (9). Both RES and PES differ from pf-RES in that they contain durable polymers, which serve to extend the duration of drug release but remain as permanent implants capable of provoking their own inflammatory responses in the arterial wall. In contrast, pf-RES contains no polymer but instead consists of 316L stainless steel microporous surface onto which rapamycin is directly sprayed (10).

In animal models, the duration of drug release of the 3 systems is very different. Wessely et al. (10) demonstrated in the porcine model that pf-RES elute two-thirds of their drug in the first week and nearly all of the loaded dose by 21 days, whereas RES stents elute only 68.4% at 28 days (3,10). Moreover, tissue levels peak at 3 days with pf-RES as compared with 14 days with the RES. The temporal release of PES is quite different with a slow release occurring over at least 28 days with the rest “sequestered within the polymer.”

These release kinetics translate into very different arterial histologic responses. Although the initial response to polymeric RES and PES is a significant decrease in neointimal growth at 28 days compared with BMS, both stents demonstrate increases in intimal formation beyond this time point such that the initial antirestenotic benefit is lost, which was also reinforced by clinical studies (11,12) (Fig. 1). Although no long-term data exist in animal models for pf-RES, responses resemble that of the BMS with similar amounts of fibrin deposition, inflammation, and endothelialization at 28 days in the porcine and rabbit models (10). These data raise the question of whether the biological effect of

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pf-RES exists or not. In general, both in humans and in animals, BMS results in an early peak in intimal formation with regression of neointima thereafter (13,14). There is no reason to suspect that the response to pf-RES would be any different than BMS, as was seen histologically in our laboratory.

Two factors are likely responsible for the differing pattern of neointimal growth seen in polymeric DES versus pf-RES. These are differences in duration of drug release and inflammatory responses to polymer. The short duration of drug release in pf-RES essentially translates into BMS-like responses with complete healing at 28 days in animal models. In the rabbit model polymeric RES demonstrate significantly increased fibrin and decreased endothelialization when compared with BMS. These data indicate that, for polymeric DES, arterial healing is complete at 28 days and that unlike BMS arterial repair continues beyond this time point. Therefore it is not surprising that, in humans, changes in neointimal growth occur far beyond the normal time point at which healing is complete in BMS (i.e., 6 months).

In addition, the durable polymers on RES (polyethylene-co-vinyl acetate [PEVA] and poly n-butyl methacrylate [PBMA]) and PES (poly[styrene-b-isobutylene-b-styrene]) provide an additional factor that influences local responses and might alter processes involved in neointimal formation. Each polymer provokes a distinctive inflammatory response in animals. In an overlapping rabbit model of stent deployment, we previously reported that RES implants were characterized by giant cell infiltration around stent struts, whereas PES provoked a heterophil/eosinophilic reaction (15). The porcine model demonstrates a progressive granulomatous and eosinophilic reaction to Cypher stent starting at 28 days and increasing out to 1 year (14). The likely explanation for these findings is a local hypersensitivity reaction to the nonerodable polymers used on the Cypher stents (PEVA and PBMA), because it peaks only after the complete release of drug (i.e., >60 days).

Carter et al. (4) have also reported similar findings in the porcine model, with western blot of stented porcine coronary arteries at 90 days demonstrating ongoing cellular proliferation despite elevation of p27kip1, a mediator of the antiproliferative effects of rapamycin. These data support the notion that polymers in DES might provoke chronic inflammation, which might be a potential driver of intimal formation, diminishing over a long term with decreased efficacy of these systems.

In contrast, pf-RES provoke little if any inflammatory reaction in animal models, but they also do not delay healing...
compared with BMS in the rabbit model. Although supporting the biocompatibility of this system, these data call into question the clinical antirestenotic efficacy reported by Byrne et al. (7). Previous nonpolymeric delivery of paclitaxel with a different system as reported by Park et al. (16) associated with less neointimal formation at 6 months, but this benefit was lost at 2 years especially in the high-dose paclitaxel arm. Heterogeneity of patient characteristics and lesions in the study by Byrne et al. complicates its interpretation, especially given that there were 2 follow-up time points. It is entirely possible that the characteristics of each group at early and late follow-up were different between stent arms, especially because patients who underwent revascularization were excluded for late follow-up analysis. In addition, the late restenosis rate is higher than has been reported by others, with composite in-segment binary restenosis being 17.3% for RES, 16.6% for pf-RES, and 21.8% for PES.

In summary, we believe these data support the notion that the vascular responses to pf-RES result in less delay in healing and diminished inflammatory responses compared with RES or PES but might be burdened with fewer efficacies. We can surmise that the data of Byrne et al. support the concept that, although DES delay intimal formation and healing, they do not halt it. As seen in animals, the 2 primary mechanisms responsible for driving the increase in intimal formation between 6 to 8 months and 2 years in humans is likely: 1) ongoing arterial repair that is accelerated in the face of decreasing drug levels; and 2) chronic inflammatory responses to polymer or excessive fibrin deposition, with both processes provoking cellular proliferation.

Practically speaking, these data also inform the way we should care for patients after DES placement. Whereas the surveillance period for symptoms of restenosis in patients receiving BMS is usually <6 months, clinicians need to be aware that polymeric DES have altered the temporal course of restenosis. In the study of Byrne et al. (7), of the 1,471 non-restenotic lesions at 6 to 8 months, 12% met the criteria for binary angiographic restenosis at 2 years, which is higher than that reported at 6 to 8 months, whereas pf-RES had higher restenosis at 6 to 8 months, but the restenosis did not increase at 2 years. These data highlight the need for continued surveillance in these patients well beyond that needed for patients receiving BMS and reminds us that, as we enlarge our understanding of DES technology, continued refinements in the care of these patients are needed.

**Key Words:** drug-eluting stents ■ polymer-free, restenosis ■ late catch-up.

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