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EDITORIAL COMMENT

Unraveling the Biological Effects of Drug-Eluting Stents*

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Intracoronary stent therapy for obstructive coronary atherosclerosis has come a long way since the first stent was developed in the 1980s. Although balloon angioplasty allowed percutaneous revascularization with a high degree of success, acute complications including flow-limiting dissections occurred frequently enough to stimulate research into more secure scaffolding to preserve the luminal enlargement created by balloon dilation. Metallic stents almost completely eliminated the acute complications of balloon dilation, but unwittingly stimulated a vascular response that included a proliferative intimal response in almost one-fourth to one-third of stented patients. This clinical limitation of metallic stents stimulated tremendous research into the biology of vascular injury, resulting in recognition of the role of "tor" (target of rapamycin) that served as the site of action of the antiproliferative agent sirolimus, the first drug used in the now historical first-generation sirolimus-eluting stent (SES), Cypher. Once again, SES achieved the almost complete suppression of neointimal hyperplasia, but at the expense of altering normal vascular healing and stimulating inflammatory changes with enhanced thrombogenicity in a minority of patients. The current generation of drug-eluting stents (DES) changed each of the components of the drug-eluting system: lower drug dose with a more efficacious release pattern, thinner metallic struts, and more biologically compatible polymers to store and release the drugs. The clinical efficacy and safety of these newer stent systems have been demonstrated in multiple clinical trials.

Despite the clinical success of the current generation of DES, the pathway to their development as outlined above highlights some of the challenges and limitations of the scientific foundation on which percutaneous mechanical treatment of obstructive coronary disease is based. The desire to improve these therapies has driven research into many diverse fields relevant to stent therapy including vascular responses to injury, thrombosis, biochemistry, polymer chemistry, and metallurgy. Given the complexity of the biological processes occurring in an atherosclerotic vessel, not to mention the vascular response occurring after stent therapy, it is not surprising that animal models precisely mimicking events in humans have been difficult to develop and validate. The relative paucity of animal models allowing precise, systematic analysis of biological processes is reflected in the clinical history of stent therapy development and makes refinement of current generation of stents challenging. Nonetheless, animal models have been useful in evaluating certain aspects of the biological response to injury of a coronary artery such as occurs with placement of a DES.

SEE PAGE 281

In this issue of *JACC: Cardiovascular Interventions*, Nishimiya et al. (1) address the issue of the role of the polymer coating of a DES in the inflammatory response to its presence, as well as the potential abnormal vasoconstrictive responses observed in the presence of the DES. The inflammatory and thrombotic responses after first-generation DES in autopsy series have been well documented by Virmani et al. (2). However, the causative agent could not be delineated from these studies. Nishimiya and colleagues (1) also highlight a growing body of recent literature that identifies an incidence of angina in up

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to one-fourth of patients with a successful DES procedure, as well as abnormal vasoconstrictive responses in certain types of DES. Moreover, there are scattered reports of a higher incidence of stent thromboses in patients with an abnormal vasoconstrictive response after DES placement. To this point, it is not known what portion of a DES is responsible for the abnormal coronary vasomotion, although limited data suggest that the polymer coating may play an important role. Using a porcine model, the authors randomly implanted 4 types of stents in the left anterior descending and left circumflex coronary arteries: a polylactic acid (PLA)–polymer coated stent that degrades in 6 to 9 months with sirolimus (P+D+); a PLA polymer-coated stent without sirolimus (P+D−); a novel poly-DL-lactic acid and polycaprolactone (PDLLA-PCL) copolymer-coated stent that degrades in 3 months; and the same bare metal stent (BMS) without polymer or drug.

Both P+D+ and P+D− were associated with significantly more inflammation at both the proximal and distal ends of the stents, as well as serotonin-stimulated vasoconstrictive responses than either PDLLA-PCL stent or the BMS. The authors next evaluated whether the vasoconstrictive responses to serotonin were ameliorated by a specific Rho kinase inhibitor, fasupril. Fasupril completely abolished the vasoconstrictive responses to serotonin, confirming that Rho kinase activation and signaling pathway were responsible for the abnormal vasomotion. These findings provide valuable insights into the role of the individual components of stent drug delivery systems in inflammation as well as abnormal vasoconstrictive responses. As clinical practice moves toward adoption of stent therapies with bioabsorbable polymers and/or completely bioresorbable stents scaffolds, these data should be valuable in the development of the most efficacious and safe drug delivery systems possible.

The Rho kinase signaling pathway has been implicated in a wide array of biological processes including inflammation, thrombosis, and vasomotion (3). It also contributes to the pleiotropic effect of statins. Specific Rho kinase inhibitors have been developed and used in limited clinical trials with patients (4). They have been shown to substantially reduce angina in patients refractory to traditional therapies. Although it still remains speculative whether specific Rho kinase inhibitors could be clinically useful in patients with persistent angina after successful DES implantation, the data from the current study make it appealing to consider this as a possible therapeutic target.

As alluded to earlier in this editorial, it is often difficult to track mechanisms responsible for a biological response in a single experiment or model. In this case, the authors acknowledge important considerations that will need to be addressed to generalize these observations beyond the current experimental model. The authors specifically chose a thick strutted stent model to isolate the effects of the polymer and the drug delivery. Yet today, based on experimental and clinical data showing that thin strutted metallic stents evoked less inflammation than thicker strutted metallic stents, these stents are no longer clinically used (5). Thus, the impact of thin strutted stents on the observations from this study remains to be determined. Additionally, the authors did not evaluate the impact of durable polymers such as the fluoropolymer in the everolimus-eluting stent that has been shown in animal models to evoke little inflammation (6).

The final pieces of information that remain provocative from this study are the observations surrounding the enhanced vasoconstrictive responses to serotonin, and their amelioration by the specific Rho kinase inhibitor fasudil, in the P+D+ stents. An interest in the role of vasospasm in the causation of myocardial infarction as well as a distinct mechanism for angina in certain patients spurred animal and experimental investigation into vasospasm as well as spasmolytic agents. As the mechanism of myocardial infarction became more clearly elucidated and the importance of vasospasm as a clinical entity faded, vasospasm as an important therapeutic target all but faded from clinical investigation. Interest in abnormal vasoconstrictive responses has once again arisen as several different clinical observations point toward an important clinical role for abnormal vasomotion after placement of current-generation stents (7). Although the final chapter(s) in this story remains to be told, Nishimiya et al. (1) have provided a small but important piece of the puzzle.

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JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 3, 2016
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