Pathology of Endovascular Stents

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KEYWORDS

• Coronary artery disease • Pathology • Bare metal stent • Drug-eluting stent • In-stent restenosis • In-stent thrombosis • Atherosclerosis • Neoatherosclerosis

KEY POINTS

- Improvement in endovascular stent performance has occurred iteratively over decades and highlights the ability to optimize physiologic function and minimize pathologic response through design.
- Pathology associated with endovascular stents most commonly manifests clinically as progressive angina due to in-stent restenosis (ISR) or acute myocardial infarction (MI) due to in-stent thrombosis (IST).
- ISR is mediated by neointima hyperplasia due to a complex interaction of biological, mechanical, technical, and patient-specific factors.
- Delayed arterial healing and possibly incomplete stent coverage by endothelium predominantly mediate IST, leading to plaque fissuring and rupture.
- Neoatherosclerosis develops over months to years as opposed to decades with native coronary atherosclerosis and contributes to late and very late IST (VLST).

INTRODUCTION

Coronary artery disease (CAD) represents the leading cause of death worldwide, attributed to more than 17.5 million deaths annually, accounting for approximately 1 of every 3 deaths.[1] In the United States, contemporary decreases in CAD-related mortality correlate with the 2 decades after the Surgeon General report on the ills of tobacco, the Framingham Heart Study identification of cardiac risk factors with lifestyle modification, and the widespread acceptance and accessibility of evidence-based use of percutaneous coronary intervention (PCI).[2] The technologies underpinning PCI have evolved iteratively from balloon angioplasty to increasingly advanced metallic stent platforms with various drug chemistries to self-degrading nonmetallic scaffolds. Large-scale clinical trials have validated the safety and efficacy of successive generations of stents. Equally important preclinical[3–5] and pathology studies provide complementary insight to reconcile adverse events; refine clinical protocols, such as optimal use of antithrombotic therapy; and drive innovation for development of next-generation stents.

NATIVE CORONARY ARTERY DISEASE

The fundamental pathogenesis of native coronary atherosclerosis has been described for decades but only recently have the specific

Financial Disclosure: Nothing to disclose for all authors.
Funding: This article was supported in part by the National Institutes of Health (R01 GM-49039) to Dr E.R. Edelman.
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Intervent Cardiol Clin 5 (2016) 391–403
http://dx.doi.org/10.1016/j.iccl.2016.02.006
2211-7458/16/$ – see front matter

nuances of these processes been characterized, particularly with respect to coronary intervention. As early as the 1970s, the importance of arterial injury in the establishment of atherosclerosis was recognized in the context of vascular smooth muscle cell activation and proliferation.[6,7] The injury model shifted toward a more complex understanding underpinned by inflammation and integration of recognized cardiac risk factors, such as hyperlipidemia, hypertension, diabetes, and smoking.[8,9] The pathogenesis of atherosclerosis as a chronic inflammatory disease marked by progressive vascular wall injury became further defined and synchronized with clinical events, such as plaque rupture and acute thrombosis comprising the acute coronary syndrome.[10–13] Establishment and maturation of atherosclerotic plaque is now well recognized as a progression from deposition and subsequent oxidation of free cholesterol, intimal thickening, and xanthoma (fatty streak) development to infiltration and lipid-avid macrophages, formation of a necrotic core, and progression to fibroatheroma predisposed to rupture and thrombosis.[14,15] Introduction of routine PCI transformed the management of CAD and provided serial clinical data that emphasized the nonlinear nature of atherosclerotic plaque development: luminal stenosis alone is not a predictor of future clinical events[16] and bore the concept of the "vulnerable plaque."[17] Not all plaques are created equal and some are more prone to rupture than others. Contemporary understanding of atherosclerosis now classifies the vulnerable plaque as thin-cap fibroatheroma (TCFA), predisposed to acute plaque rupture, and incorporates other pathologic mechanisms of thrombosis, such as healed plaque rupture, surface erosion, and calcified nodules.[13] Antemortem identification of such rupture-prone plaques has yet to be realized, frustrating current clinical management paradigms and causing some investigators to question the very existence of such lesions.

PATHOLOGY OF BALLOON ANGIOPLASTY

The introduction of PCI with balloon angioplasty marked the first widely adopted technique to directly alter the natural history of atherosclerosis. Angioplasty alone, however, proved a temporizing therapy, owing to the traumatic and inconsistent nature of plaque modification.[18–20] Although initially perceived and perhaps hoped to result in permanent deformation, the end result was far more elastic, with reversible displacement that more often recoiled back to its original dimension. Associated tissue damage was, however, real and injury to endothelium, intima, and media promoted rapid restenosis within weeks to months of therapy in addition to further precipitating the acute complications of arterial dissection and recoil.[21,22] The specific effects of balloon angioplasty on the arterial wall have been defined serially: vascular recoil and contraction after balloon dilation; injury to the intima and dissection of the media; and inflammatory activation and proliferation of vascular smooth muscle cells, resulting in rapid neointimal hyperplasia, extracellular matrix deposition, and negative vascular remodeling.[23–26] To combat the loss of effect and minimize the extent of injury, PCI incorporated the use of permanent metal mesh implants—bare metal stents (BMSs)—after balloon angioplasty to rigidly support the arterial lumen, control arterial dissection, and prevent acute arterial recoil to good effect.[22,27] Stent placement, nevertheless, necessarily modifies the stenotic lesion and alters arterial architecture, inducing arterial injury not unlike balloon angioplasty.

PATHOLOGY OF BARE METAL STENTS

BMS deployment typically results in neointimal hyperplasia, which is driven by vascular smooth muscle cell proliferation and associated with macrophage accumulation and neovascularization. Neointimal hyperplasia may be distributed either along the length of the stent or focally.[24,28–34] During the first 2 weeks of BMS placement, fibrin, platelets, and acute inflammatory cells are localized to the stent struts, in particular those embedded within the necrotic plaque core or injured arterial wall media (**Figs. 1** and **2**).[35,36] In the weeks and months that follow, neointimal hyperplasia and then, increasingly, extracellular matrix deposition contribute to neointimal growth.[37] In association with a metallic scaffold, the arterial architecture is altered such that homeostatic expansive remodeling occurs (the so-called Glagov phenomenon[38]) and physiologic vasodilation is impaired. Incremental plaque development thus directly impinges on lumen area, rapidly precipitating ISR at an accelerated rate compared with native disease. Through these mechanisms, ISR accelerates early and seems to peak at approximately 6 months and, in its ultimate state, may precipitate recrudescence of clinical symptoms requiring repeat target lesions revascularization (TLR). By the first year after BMS placement, however, the neointima generally stabilizes and luminal diameter