Coronary Artery Restenosis: Vision to the Future

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Over the past 15 years, our understanding of the pathophysiologic mechanisms of percutaneous angioplasty, including the biologic response to vessel injury, has evolved rapidly. The concept of controlled plaque dissection by balloon angioplasty, as well as the salutary effects provided by stent deployment utilizing metal scaffolding of dissected plaque components that optimize laminar flow characteristics and prevent elastic recoil, have been delineated. Advances in operator technique to optimize procedural stent deployment, along with new adjunctive procedural pharmacotherapy, have minimized the frequency of subacute stent thrombosis. Indeed, through understanding the pathogenetic role of the blood platelet and the advantages of combination strategies for platelet inhibition in preventing stent thrombosis, the practice of aggressive anticoagulation has been discarded and bleeding complications associated with coronary stent deployment reduced. In addition, the mechanisms of vessel injury by percutaneous coronary intervention (PCI), particularly stent deployment, have recently been described.

Although stents maximize the initial (procedural) arterial lumen gain when compared with standard balloon angioplasty, the late lumen loss elicited by the metal prosthesis is greater. Nevertheless, net lumen gain (initial gain − late loss) at late follow-up (6-12 months) is greater following stent (compared with balloon) deployment for moderate to large caliber vessels (> 3.0 mm reference diameter). However, exaggerated late lumen loss resulting in recurrent stenosis, or restenosis, has become the main limitation of stenting. Basic and clinical research efforts have focused on the mechanism of intraluminal neointimal tissue formation and the respective roles played by thrombus, inflammation, smooth muscle cell migration/proliferation, extracellular matrix formation, and subsequent re-endothelialization with healing. Focal targets for strategies aimed

toward interrupting this process have been identified. Innumerable clinical trials followed, examining systemically administered agents designed to suppress the inflammatory or neointimal proliferative response provoked by stent deployment. None proved dramatically successful and, subsequently, the concept of targeted drug delivery to the site of vessel injury was proposed. This concept of providing high local (tissue) concentrations of an agent while minimizing/eliminating systemic toxicity was intuitively attractive. Thus, various agents which interrupt the cell cycle were placed on various stent-based platforms. This strategy continues to evolve and involves polymer as well as non-polymer elution systems, in addition to metal and non-metal alloys, as well as bioabsorbable stent platforms. Despite theoretic appeal and/or preliminary results in animal models, not all pharmacologic agents have been successful in combating the restenosis process following stent deployment in man. The concepts underlying design and development of stent-based drug delivery systems are outlined in this supplement by Dr. Campbell Rogers. Dr. Rogers provides the rather unique combined perspectives of a clinical interventionalist and basic scientist.

Furthermore, the best drug and drug-delivery platform for suppressing restenosis is effective only if it can be delivered to the site of target stenosis. Thus, the concept of target lesion preparation to ensure stent delivery and optimal deployment remains important in the era of drug-eluting stents. Indeed, inadequate or suboptimal stent expansion has been incriminated in late failure (restenosis) of drug-eluting stents. Drs. Jeffrey R. Moses, Stephane Carlier, and Issam Moussa provide a contemporary update on ablative and non-ablative techniques for target lesion preparation to optimize drug-eluting stent deployment. In addition, the initial human clinical experience with stent-based delivery of everolimus is summarized by Drs. Eberhard Grube and Lutz Buellesfeld. Dr. Grube has been intimately involved in the initial clinical evaluation of multiple drug-eluting stent designs. The initial clinical trial experience with the everolimus-eluting stent demonstrates marked efficacy for suppression of neointimal proliferation with very low values for late lumen loss and binary (> 50%) angiographic restenosis.

Through examination of the evolution of PCI and coronary stenting, the inverse relationship between reference vessel diameter and late restenosis is readily apparent. This relationship persists in a more muted fashion in the era of drug-eluting stents. With intrinsically higher rates of late restenosis following either balloon angioplasty or bare-metal stenting, small vessel PCI has been problematic. Performance characteristics intrinsic to the stent platform itself, further influenced by the polymer-drug coating, may materially affect the deliverability of the drug-eluting stent device to the small vessel target. Issues of stent strut thickness and metal alloy composition may significantly contribute to device profile, flexibility, and deliverability to small vessels, which are often more peripheral and tortuous. Thus, the optimal drug-eluting stent for small vessel application will likely combine all of the advantages of bare-metal stent design as well as targeted pharmacology.

As interventional cardiologists, we currently treat only severe, fibrocalcific stenoses. This subset of lesions represents only the tip of the iceberg for coronary atherosclerosis and, in fact, does not include the majority of patients who suffer acute myocardial infarction or sudden cardiac death. Indeed, most victims of these catastrophic events have an underlying offending stenosis of less than 70% severity. The characteristics of such so-called vulnerable plaque have recently been elucidated and are succinctly summarized by Drs. Mamoo Nakamura, David P. Lee, and Alan C. Yeung. We have only begun to understand the complex relationship between vulnerable plaque and vulnerable patient. The detection and treatment of vulnerable plaque represents an exciting new frontier in cardiovascular medicine. Although targeted or regional drug delivery will likely maintain a position of central importance in the treatment armamentarium for vulnerable plaque, the need for metal alloy scaffolding of softer, sub-critical stenoses is much less clear. Indeed, several other technologies aimed at targeted apoptosis of inflammatory and/or proliferative plaque components have generated considerable interest.

In summary, this supplement provides a broad view of recent advances in PCI, particularly drug-eluting stent therapy, as well as valuable insights into the pathophysiology of vulnerable plaque and the potential options for its treatment. I would like to congratulate our expert panel on their extremely current, leading-edge contributions, which are tempered by the perspective of clinical experience. I am grateful to the Guidant Corporation for generously providing their financial support for this important project. ■