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EDITORIAL

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Percutaneous coronary intervention for cardiac transplant vasculopathy

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Orthotopic heart transplantation represents one of the greatest advances of current medical science, with the potential to restore health to otherwise moribund individuals with end-stage cardiac disease. The transplant procedure, however, does not represent a "cure", as patients require lifelong therapy with potent immunosuppressant medications and constant surveillance for life-threatening complications including allograft rejection and infection. Following transplantation, patients are also highly prone to the development of an unusually aggressive and rapidly progressive form of coronary artery disease often termed cardiac allograft vasculopathy (CAV), which represents the leading cause of death among heart transplant patients following the first post-transplant year [1]. CAV appears to result from a combination of immune-mediated and non-immunologic factors that result in endothelial cell injury, thereby precipitating vascular smooth muscle cell proliferation and subsequent intimal thickening. The presence of CAV can be detected in up to 50% of patients within 5 years of transplantation, and following the detection of CAV 5 year survival falls to only approximately 20% [2].

The diagnosis of CAV is problematic, as denervation of the transplanted heart typically eliminates the anginal warning system. Because non-invasive tests have proved unreliable for the detection of transplant coronary disease, most transplant centers perform yearly surveillance coronary angiography to screen for and follow the progression of CAV. Coronary angiography itself tends to underestimate the extent of CAV due to the diffuse nature of the process. While focal severe coronary lesions can occur and serve as targets for percutaneous coronary intervention (PCI), intravascular ultrasound imaging has demonstrated that CAV is typically a diffuse, concentric process that involves the entirety of the coronary tree from larger proximal vessels to small distal branches [3, 4].

Several institutions have reported their experiences with PCI for CAV, although the ultimate impact of PCI on survival following heart transplantation remains uncertain [5]. PCI for the treatment of severe focal lesions is associated with high initial success rates, but restenosis following either balloon angioplasty or stenting is much more common in the post-transplant population than among non-transplant patients undergoing PCI for atherosclerotic coronary disease. Among 65 transplant patients who underwent PCI at The University of California at Los Angeles, for example, procedural success was achieved in 93% of individuals, however angiographic restenosis rates were 56% following balloon angioplasty and 31% following bare-metal stenting. Drug-eluting stents were used in a small number of patients and yielded a restenosis rate of 19%, however experience and late follow-up with drug-eluting stents for the treatment of CAV remains extremely limited [6].

Techniques for the performance of PCI among patients with CAV have traditionally mirrored those of PCI for non-transplant patients with atherosclerotic coronary disease. In the current issue of "Cardiology Journal", Aqel et al. [7] report on their institution's experience using the direct thrombin inhibitor bivalirudin during PCI for CAV. Randomized multicenter trials have demonstrated that

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the use of bivalirudin during PCI among patients with stable and unstable coronary syndromes is efficacious and associated with a lower likelihood of bleeding complications than the use of combination therapy with unfractionated heparin and platelet glycoprotein IIb/IIIa receptor antagonists [8, 9]. This finding has been surprising to some, as longstanding belief has held that thrombotic complications resulting from PCI are primarily platelet-mediated, and whereas IIb/IIIa antagonists serve as potent inhibitors of platelet function, bivalirudin acts principally to inhibit fibrin clot formation and impairs platelet function only indirectly. It is important to note that in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study, the largest randomized trial of bivalirudin versus IIb/IIIa antagonist therapy during PCI, the efficacy of bivalirudin among patients with acute coronary syndromes was dependent upon the coadministration of the oral platelet inhibitor clopidogrel prior to PCI. Patients in the trial who received bivalirudin without clopidogrel pretreatment demonstrated significant 29% increase in ischemic events compared to patients treated with a IIb/IIIa antagonist, supporting the need for antiplatelet therapy during higher risk PCI [9].

While the efficacy of bivalirudin compared to the IIb/IIIa antagonists in the setting of PCI for thrombus laden atherosclerotic lesions such as those found with acute myocardial infarction remains controversial, bivalirudin does seem well suited for use during PCI of the smooth, hyperplastic lesions associated with CAV. Among the 30 patients described by Aqel et al. [7] who underwent a total of 51 PCI procedures using clopidogrel pretreatment and intra-procedural bivalirudin, the 30-day incidence of death, MI, or need for target revascularization was zero, and the incidence of major bleeding events at 30 days was 3.9%. While this retrospective, uncontrolled analysis is not adequately powered to provide definitive conclusions, these low initial complication rates compare favorably with results achieved in larger trials of bivalirudin therapy during PCI for atherosclerotic coronary disease, and support further investigation in the post-transplant population.

In the end, while PCI has the potential to lower ischemic burden stemming from severe focal stenoses arising after heart transplantation, it is vital to remember that CAV represents a diffuse relentless disease process. Medical therapies aimed at prevention of this disseminated process ultimately represent the best hope for therapy. Several agents including statins, sirolimus, everolimis, and diltiazem have been associated with significant reductions in the incidence of CAV, and other agents will likely emerge as the mechanisms of CAV become better understood. Until such time, specific investigations to better define the indications and optimize the safety and efficacy of PCI following heart transplantation, such as that of Aqel et al. [7], remain essential.

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