A djunctive platelet glycoprotein (GP) IIb/IIIa receptor inhibition during percutaneous coronary intervention (PCI) reduces the incidence of periprocedural major adverse cardiovascular events and improves long-term clinical outcomes. The specific administration of abciximab has been associated with a long-term (1 to 3 years) survival advantage that seems to be proportional to the preprocedural clinical risk profile of the patient. Initial reports that abciximab administration during PCI for surgical bypass grafts reduced the incidence of distal embolization and improved late clinical outcomes were embraced enthusiastically by interventional cardiologists because of the problematic nature of PCI in this complex subset of patients.

Compared with native coronary vessel PCI, surgical bypass graft intervention is associated with an increased frequency of periprocedural myocardial infarction, as well as an increased incidence of recurrent ischemia, repeat revascularization, and mortality in late follow-up. Indeed, multivariable analysis demonstrates a history of prior coronary bypass graft surgery to be an independent correlate of mortality to 3 years after PCI, which likely reflects the more generalized burden of atherosclerotic disease process in this population. Despite the initial enthusiasm for adjunctive platelet GP IIb/IIIa blockade during bypass graft PCI, subsequent reports have questioned the effectiveness of this strategy. The article by Roffi et al in the current issue of Circulation confirms and extends the knowledge base on adjunctive pharmacotherapy during bypass graft PCI and fits nicely into our current framework of understanding provided by parallel evolution in concepts regarding the pathophysiology of atheroembolization and the benefit provided for nonpharmacological mechanical embolic protection devices. These recent revelations demand a unified reappraisal of the field.

First, what do we know about atherosclerotic disease of bypass grafts and the pathophysiology of atheroembolization? Atheroma from saphenous vein bypass grafts is friable, soft, lipid-rich, and often accompanied by overlying organized thrombus. This histopathological substrate is prone to fragmentation and embolization during PCI. Both aspirate and filter analyses after early clinical experience using distal embolic protection devices for vein graft PCI have provided an insightful profile of this atherothrombotic debris. Debris particle size shown by scanning electron microscopy reveals that >80% of particles are <100 μm in diameter. Further characterization by the least bounding rectangular model, which derives the major and minor axes for each particle, demonstrates a total particulate volume per filter of 26±22.5 mm³ (mean±SD) with a range of 2 to 83 mm³. Although smaller particulate debris may be better tolerated with respect to mechanical obstruction and reduction of regional myocardial blood flow (similar effect for 10³ particles at 15 μm versus 10⁴ particles at 100 μm versus 10 particles at 300 μm), plaque embolization catalyzes a complex interaction also involving microvascular spasm and thrombosis (Figure 1). The ultimate expression of this multifactorial process is the development of the “no-reflow” phenomenon in 5% to 10% of vein graft PCI. Histological composition of vein graft aspirates after PCI demonstrates a prevalence of fibrin (100%), necrotic atheromatous core (100%), foam cells (80%), and cholesterol clefts (30%) (Figure 2). These observations are consistent with intravascular ultrasound-determined plaque morphology in patients who experience atheroembolization/no reflow after PCI to treat evolving myocardial infarction. Ultrasound characterization of a predominant “lipid-pool”-like image from vessels with larger...
cross-sectional areas supports a similar pathophysiological process after native vessel PCI. Furthermore, coronary ultrasound-demonstrated plaque size reduction after PCI in patients with unstable angina or acute myocardial infarction likely reflects disgorgement of plaque material and subsequent embolization in addition to plaque compression or redistribution. Microvascular plaque embolization demonstrated noninvasively by MRI, contrast echocardiography, or single photon emission computed tomography has adverse clinical prognostic implications. Is it likely that any single prophylactic therapeutic approach to atheroembolism will be 100% effective, when the pathogenesis of this syndrome is so diverse? The answer to this question is intuitively obvious. Patients randomly allocated to PercuSurge (Medtronic) embolic protection (versus standard care without embolic protection) during vein graft PCI in the Saphenous vein graft Angioplasty Free of Emboli Randomized trial (SAFER) still incurred an appreciable incidence of adverse periprocedural events to 30 days, including death (1%), Q or non-Q-wave myocardial infarction (8.5%), no reflow (3.4%), and overall major adverse cardiovascular events (9.6%). Indeed, the combined occurrence of death or myocardial infarction to 30 days after PCI despite embolic protection (9% to 10%) is comparable to that observed in placebo-treated patients from randomized controlled trials of platelet GP IIb/IIIa receptor inhibition for native coronary vessel stenting. Although adjunctive prophylactic GP IIb/IIIa inhibition therapy was administered (nonrandomized allocation) to ≥60% of patients enrolled into the SAFER trial, a similar magnitude of adverse cardiovascular event reduction was provided by mechanical embolic protection whether GP IIb/IIIa inhibition was administered (18.1% to 10.8%) or not (14.1% to 8.0%). This observation attests to the diverse pathogenesis of atheroembolism and the preeminent importance of mechanical microvascular obstruction. Currently available technologies (or those in clinical testing) for per-PCI embolic protection have focused either on conduit occlusion with subsequent aspiration or on distal filter capture of debris. Because of intrinsic limitations, protection provided by these technologies will not be “complete.” Causes of incomplete embolic protection include device crossing profile (larger profiles promote embolization), incomplete conduit occlusion or filter apposition, incomplete aspiration, filter pore size (either too large or small), device-mediated intimal trauma, side branches (“backwash” during occlusion versus siphoning of debris during filter) and delayed platelet-white cell embolization from the target site.

A novel approach under investigation that may circumvent many of these limitations involves proximal conduit occlusion (before crossing the target lesion) and uses gentle distal coronary pressure-driven aspiration to evacuate particulate debris irrespective of particle size or side branch location. This technology (Proxis, Velocimed) also provides access to the distal microcirculatory bed to allow prophylactic administration of cardioprotective or nutrient solutions and thus facilitates a multifaceted (pharmacomechanical) approach to address this complex pathophysiological process. Indeed, co-administration of agents that enhance ischemic tolerance, improve myocardial energetics, or relieve microvascular spasm will likely provide incremental benefit to that provided by mechanical embolization protection alone. The importance of microvascular spasm in the pathophysiology of atheroembolization and no reflow is confirmed by the beneficial treatment effect demonstrated for “small vessel” vasodilators (calcium channel blockers, adenosine, sodium nitroprusside) and the reduction in no reflow when verapamil is administered prophylactically before PCI.

What does the work of Roffi et al teach us? First, it confirms previous, less robust observations that patients with prior coronary bypass surgery have more frequent adverse clinical events, including death, after PCI. Second, for all of the pathophysiological reasons discussed previously, adjunctive platelet GP IIb/IIIa receptor inhibition does not provide clinical benefit for PCI in this patient population. A pivotal third observation by Roffi et al is that more than half of all subsequent ischemic events occur beyond 30 days after PCI. This finding attests to the importance of secondary preventative measures in patients with prior bypass graft surgery and of the fact that only half or fewer of the patients analyzed in this study were receiving lipid lowering therapy, angiotensin converting enzyme inhibitors or β-blockers at the time of hospital discharge. The authors have nicely addressed the statistical limitations inherent to pooled analyses. Although the dose of eptifibatide used in the trials included in the present analysis provides less potent platelet inhibition than the dose currently recommend for PCI, the data for outcomes are directionally consistent with those for bypass graft patients and differ from those observed in the general PCI population.

How do we apply the findings of Roffi et al to our practice? This study does not provide data on the presence or magnitude of clinical benefit provided by platelet GP IIb/IIIa inhibition when administered as adjunctive therapy during mechanical embolic protection. Indeed, blockade of platelet aggregation and the formation of platelet-white cell aggregates could enhance filter pore efficiency and reduce the
likelihood of filter obstruction. In addition, the specific antiinflammatory21 or cytoprotective effects22 of abciximab, which have been implicated in conferring a late survival advantage after administration of this agent for PCI, are not negated. The analysis by Roffi et al is neither adequately powered nor of adequate duration follow-up to assess late survival. The work of Roffi et al10 serves mainly to underscore the dominant pathogenetic influence of mechanical debris obstruction and the residual inadequacies of current periprocedural antithrombotic therapy during bypass graft PCI. This work provides direction for further investigation.

References

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