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.\(^1\) The specific administration of abciximab has been associated with a long-term (1 to 3 years) survival advantage\(^2,3\) that seems to be proportional to the preprocedural clinical risk profile of the patient.\(^4\) 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.\(^5,6\)

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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.\(^7\) Indeed, multivariable analysis demonstrates a history of prior coronary bypass graft surgery to be an independent correlate of mortality to 3 years after PCI,\(^4\) 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.\(^8,9\) The article by Roffi et al\(^10\) 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 integration for 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.\(^11\) 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.\(^12,13\)

Debris particle size shown by scanning electron microscopy reveals that >80% of particles are <100 \(\mu\)m 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 \(26\pm22.5\,\text{mm}^3\) (mean\(\pm\)SD) with a range of 2 to 83 \(\text{mm}^3\).\(^14\) Although smaller particulate debris may be better tolerated with respect to mechanical obstruction and reduction of regional myocardial blood flow (similar effect for 10\(^3\) particles at 15 \(\mu\)m versus 10\(^5\) particles at 100 \(\mu\)m versus 10 particles at 300 \(\mu\)m),\(^15\) 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.\(^2,16\) 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).\(^12,13\) These observations are consistent with intravascular ultrasound-determined plaque morphology in patients who experience atheroembolization/no reflow after PCI to treat evolving myocardial infarction.\(^17\) Ultrasound characterization of a predominant “lipid-pool”-like image from vessels with larger

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** The pathophysiology of no-reflow is multifactorial and involves varying degrees of vasospasm, thrombosis, and mechanical plaque embolism. Various agents demonstrated to be efficacious in relieving microvascular vasospasm include calcium-channel blockers, adenosine (adenocard), and sodium nitroprusside. Conversely, nitroglycerin, which dilates epicardial vessels, has limited efficacy. Similarly, platelet aggregates, white cell platelet aggregates, and thrombus have all been implicated in this process. Various strategies aimed at reducing mechanical plaque embolism have included direct stenting, covered stent grafts, and embolic protection devices.
single photon emission computerized tomography has ad-
strated noninvasively by MRI, contrast echocardiography, or
PCI embolic protection have focused either on conduit
tance of mechanical microvascular obstruction. Currently
pathogenesis of atheroembolism and the preeminent impor-
tance of mechanical microvascular obstruction. Currently
available technologies (or those in clinical testing) for peri-
PCI embolic protection have focused either on conduit
occlusion with subsequent aspiration or on distal filter cap-
ture 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), in-
complete conduit occlusion or filter apposition, incomplete
aspiration, filter pore size (either too large or small), device-
mated 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 occlu-
sion (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 admin-
istration of cardioplegic or nutrient solutions and thus facil-
itates a multifaceted (pharmacomechanical) approach to ad-
dress 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 atheroem-
bolization 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 adminis-
tered prophylactically before PCI.

What does the work of Roffi et al\textsuperscript{10} 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, adjunc-
tive 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\textsuperscript{10} is that more than half of all
subsequent ischemic events occur beyond 30 days after PCI.
This finding attests to the importance of secondary prevent-
tive 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 \(\beta\)-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 pa-
tients and differ from those observed in the general PCI
population.

How do we apply the findings of Roffi et al\textsuperscript{10} 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 aggre-
gates 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

Key Words: Editorials ■ glycoproteins ■ embolism ■ angioplasty
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