Delivery of Glycoprotein IIb/IIIa Inhibitor Therapy for Percutaneous Coronary Intervention
Why Not Take the Intracoronary Highway?

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A major goal of any antithrombotic regimen administered during percutaneous coronary intervention (PCI) is the preservation of coronary microvascular perfusion, which is critical for myocardial survival. In addition to macrovascular thrombosis, microembolization into the downstream coronary artery bed that occurs during spontaneous plaque rupture and PCI plays a prominent role in the development of microvascular dysfunction that leads to myocardial infarction. In addition to physical obstruction of the lumen by the embolus, vasoconstriction and edema due to inflammation also impair microvascular flow.1 These events likely occur more frequently during PCI performed in the setting of unstable coronary syndromes.2 With Doppler guidewire technology, it was estimated that an average of 25 embolic events occurred during primary PCI for ST-segment elevation myocardial infarction.3

Platelets aggregate when fibrinogen binds to the active glycoprotein (GP) IIb/IIIa receptor. There are ∼60 000 to 80 000 GP IIb/IIIa receptors on each platelet.6 GP IIb/IIIa blockers are the most potent inhibitors of platelet aggregation and act by inhibiting fibrinogen binding to the active receptor complex and subsequent platelet-platelet cross-linking. When optimally dosed, these agents induce essentially uniform platelet-inhibitory effects, measured by ex vivo conventional aggregometry and point-of-care assays, irrespective of agonist concentration and type. The latter uniformity of pharmacodynamic effect distinctly contrasts with the nonuniform and comparatively modest platelet inhibition induced by oral antiplatelet therapies. Moreover, GP IIb/IIIa inhibitors are the only available therapy that profoundly blocks thrombin-induced platelet aggregation.7 In multiple studies, the intravenous administration of GP IIb/IIIa inhibitors reduces the prevalence of peripheral myocardial infarction. In addition, GP IIb/IIIa inhibitors block platelet expression of the prothrombotic and proinflammatory mediator CD40 ligand.8

The acute effects of GP IIb/IIIa inhibitors on the preservation of microvascular perfusion have been attributed to inhibition of de novo platelet aggregation and disaggregation of platelet aggregates already formed by the displacement of fibrinogen from the receptor. Optimal dosing of a GP IIb/IIIa inhibitor to induce platelet aggregation <20% of baseline required ≥80% occupancy of the receptors by the inhibitor.9 The latter degree of receptor occupancy (RO) was also associated with inhibition of thrombosis in animal models.10 Moreover, Gibson et al11 demonstrated that higher RO was associated with restoration of epicardial flow, normal myocardial perfusion, and complete ST-segment elevation resolution in patients with ST-segment elevation myocardial infarction treated with low-dose tenecteplase and intravenous eptifibatide in a substudy of the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) trial. Importantly, it was the number of GP IIb/IIIa receptors available for cross-linking and not the absolute number of receptors bound by drug that correlated with improvements measured electrocardiographically and angiographically.11

In vitro studies have shown that the administration of all GP IIb/IIIa inhibitors in clinically relevant concentrations can clearly disaggregate newly formed platelet aggregates by displacing fibrinogen from the receptor.12,13 Moser et al12 demonstrated that eptifibatide had greater disaggregating effects than abciximab, which was attributed to superior access to the receptor by the lower-molecular-weight agent and a lower affinity for the receptor that allowed the displacement of more molecules in a given time. Disaggregating
effects were observed in the absence of any evidence of clot lysis induced by the GP IIb/IIIa inhibitor.\textsuperscript{12} In other in vitro studies of more mature platelet thrombi that used a capillary perfusion system, Speich et al\textsuperscript{13} expanded on the work of Moser et al\textsuperscript{12} and reported greater aggregate dissociation with eptifibatide than with abciximab at concentrations achieved clinically. In their experiments, the greatest dissociation occurred at the highest concentrations.\textsuperscript{13}

Thiele et al\textsuperscript{14} demonstrated that intracoronary administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary PCI was associated with decreased median infarct size (15.1\% versus 23.4\%, $P=0.01$), smaller microvascular obstruction measured by delayed-enhancement magnetic resonance ($P=0.01$), and improved myocardial perfusion measured by ST-segment resolution than the same bolus doses administered intravenously followed by an intravenous infusion. Small-molecule GP IIb/IIIa inhibitors may be associated with improved outcomes by penetrating the platelet-fibrin thrombus more effectively than the higher-molecular-weight antibody abciximab. In an earlier study, Deibele et al\textsuperscript{15} reported that intracoronary administration of a double-bolus dose of eptifibatide through the guiding catheter during PCI in 54 patients with unstable angina/non–ST-segment elevation myocardial infarction was safe. Hassan et al\textsuperscript{16} further supported the latter observations regarding safety in a larger number of patients.

In this issue of *Circulation*, Deibele et al\textsuperscript{17} have expanded their previous work with intracoronary eptifibatide delivered through the guide catheter by studying the relation of RO to myocardial perfusion. RO was measured by the D3 antibody, which binds to a ligand-induced binding site when the receptor is occupied by eptifibatide. This technique has been used in previous work by the authors to study RO by eptifibatide.\textsuperscript{15} Deibele et al provide further compelling mechanistic evidence here to support the intracoronary route for administration of eptifibatide compared with the intravenous route. In this first randomized study, patients with acute coronary syndrome undergoing PCI were treated with either intracoronary or intravenous bolus administration of eptifibatide. Compared with their previous studies, here, the drug was buffered for intracoronary administration. There were important observations made by the authors. First, there were no complications associated with the intracoronary route, consistent with prior studies of intracoronary administration. Second, there was greater RO in the local blood after intracoronary bolus administration, and as expected, the difference between the intravenous and intracoronary routes was most marked after the first bolus. Third, higher RO in the intracoronary group was associated with better post-PCI perfusion after intracoronary adenosine administration, as measured by the corrected TIMI (Thrombolysis In Myocardial Infarction) frame count, a measurement of coronary flow and microvascular perfusion that has been associated with clinical outcomes in multiple studies. For example, after fibrinolytic therapy, a lower corrected TIMI frame count was associated with better survival and greater improvement in left ventricular function after primary PCI. In the Randomized Efficacy Study of Tirolfiban for Outcomes and Restenosis (RESTORE) trial, a study of intravenous tirolfiban administration for acute coronary syndrome patients undergoing PCI, a higher corrected TIMI frame count was associated with greater mortality.\textsuperscript{18}

There are obvious limitations to the present study that are largely acknowledged by the authors. The study was a small mechanistic investigation. There were more patients in the intravenous group with ST-segment elevation myocardial infarction, which raises the question of differences in the extent of clot burden and composition, which may have contributed to the higher post-PCI corrected TIMI frame count in the latter group; thrombus burden was not quantified, although it was hypothesized by the authors that the intracoronary route would reduce it. Also, it is unknown from the present study how direct thrombus aspiration may affect the observed results. The authors also did not assess left ventricular function or measure myocardial perfusion by other established methods, and a relation between the route of eptifibatide administration to post-PCI TIMI myocardial perfusion grade and myocardial infarction could not be well studied owing to the sample size.

In conclusion, Deibele et al\textsuperscript{17} should be congratulated for conducting this first randomized study. Intracoronary eptifibatide administered before PCI to patients with acute coronary syndrome (2 boluses in 2 minutes separated by a 10-minute interval) appeared safe and produced greater local platelet GP IIb/IIIa blockade than the intravenous route, which correlated with better myocardial perfusion by 1 measurement, the corrected TIMI frame count. The responsible mechanism cannot be determined from the present study but may be greater platelet disaggregation induced by higher local doses. Given the absence of any reported hazards with this delivery method in the present study and others, future larger studies should be undertaken to verify the clinical relevance of these interesting and intuitive findings. One such study (n=530) that is enrolling patients is the Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial (ClinicalTrials.gov trial number NCT00927615). The latter study will also use thrombus aspiration and evaluate short- and long-term clinical events.\textsuperscript{19} Interventionalists may soon be choosing the intracoronary highway as the preferred route for GP IIb/IIIa inhibitor delivery in PCI patients with acute coronary syndrome.

**Disclosures**

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**References**


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