Exploring Mechanisms of Graft Occlusion

Toward Improved Outcomes in Coronary Artery Bypass Graft Surgery*

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The management and prevention of clinical events related to atherothrombosis requires negotiation of the balance between prevention of arterial thrombosis and maintenance of hemostasis. Striking the right balance is a particular challenge in patients undergoing coronary artery bypass graft (CABG) surgery in view of the imperative for securing hemostasis after surgery while avoiding potentially fatal thrombotic graft occlusion. It is well recognized that oral antiplatelet therapy is required in the long term to reduce the risk of thrombotic graft occlusion. Aspirin has proven efficacy in reducing the risk of graft occlusion (1) and has a number of advantages in this regard: it reliably inhibits its target, platelet cyclooxygenase (COX)-1, to a high level with irreversibility of effect that provides a rationale for once-daily dosing; its effects on hemostasis are limited, and therefore, it can usually be safely administered within 24 h after surgery or can be continued in the perioperative period; and it is very cheap and therefore highly cost effective (2,3).

However, a major limitation of aspirin is that COX-1 has a restricted role in platelet activation (Fig. 1), so that platelet reactivity can remain high even with complete inhibition of this enzyme (4). Consequently, it may lack efficacy under circumstances where greater inhibition of platelet function is required because of adverse local blood flow rheology or highly thrombogenic vessel wall or systemic factors. Rarely, aspirin fails to inhibit platelet COX-1 effectively, with principle factors being poor compliance, adverse interaction with nonsteroidal anti-inflammatory drugs, increased platelet turnover (making once-daily dosing suboptimal), and possibly platelet COX-2 expression. In this issue of the Journal, Gluckman et al. (5) demonstrate how reliably aspirin inhibits COX-1 in patients undergoing CABG surgery, with few patients exhibiting poor inhibition particularly during chronic administration. Despite this, platelet reactivity remains high in some patients. Higher levels of shear-induced platelet aggregation assessed by the Platelet Function Analyzer-100 collagen-adenosine diphosphate cartridge assay (Siemens Healthcare Diagnostics, Newark, Delaware), which is insensitive to COX-1 inhibition, are shown to be associated with increased incidence of graft occlusion. Because there is a rational basis for expecting high platelet reactivity to increase the risk of graft occlusion, this study provides a strong rationale for investigating alternative or supplementary targets for antithrombotic therapy beyond COX-1 for patients at higher risk of graft occlusion resulting from either rheological factors (small-diameter grafted vessel) or prothrombotic systemic factors, including high platelet reactivity. Ticagrelor, an oral reversibly binding inhibitor of the platelet P2Y₁₂ receptor, achieved greater and more consistent inhibition of platelet aggregation in acute coronary syndrome patients enrolled in the PLATO (Platelet Inhibition and Patient Outcomes) study compared with clopidogrel (6) and was associated with lower mortality in patients undergoing CABG surgery in this study (7). These findings indicate the need for further studies of P2Y₁₂ inhibition for maintaining graft patency. Protease-activated receptor (PAR)-1, a thrombin receptor present on platelets and other cells including vascular smooth muscle cells, is another promising target because inhibition has a significant antithrombotic effect, but little effect on hemostasis (8), potentially allowing therapy to be maintained throughout the operative period. Two ongoing phase 3 placebo-controlled studies of vorapaxar, a PAR-1 antagonist, in patients with acute coronary syndromes or stable atherosclerotic disease should provide some information on the efficacy and safety of this therapy in patients undergoing CABG surgery.

Another finding in this study is that increased urinary thromboxane B₂ excretion at 6 months after surgery is associated with a higher incidence of graft occlusion at this time point. Although it is possible that the graft occlusion itself is the cause of greater thromboxane A₂ production through activation of leukocytes and other cells in the thrombosed graft and other diseased grafts, the alternative hypothesis that thromboxane A₂ is linked to the causation of graft occlusion is intriguing. This raises many questions about the role that inflammatory processes, including induction of COX-2, play in the pathogenesis of graft occlusion. The adverse cardiovascular consequences of inhibiting COX-2 after CABG surgery discourage specific targeting of this enzyme in CABG patients (9), but encourage consideration of related targets that will not

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have an adverse impact on prostacyclin release from endothelial cells, an important factor in suppressing the reactivity of circulating platelets. Inflammation increases the levels of coagulation factors and von Willebrand factor, as well as potentially increasing platelet reactivity through increased platelet turnover; so, targeting appropriate signaling cascades involved in inflammation could provide a unified approach to the problem of graft occlusion. Balanced against this approach is the need to allow adequate wound healing and to avoid wound infections after surgery, which may be compromised by some anti-inflammatory therapies and could justify delayed initiation of therapy.

It is notable that a medical history of diabetes mellitus was not associated with early graft occlusion in this study, consistent with the results of previous studies. Diabetes mellitus is associated with a tendency toward higher platelet reactivity, higher levels of procoagulant factors, greater systemic inflammation, and reduced efficacy of aspirin (10,11), and consequently some signal of increased graft failure in diabetic individuals may be expected. The lack of such a signal to date suggests a complexity to the pathobiology of graft disease or perhaps a beneficial effect of hypoglycemic medication. Further prospective studies of even greater size and complexity are required to examine further the influences of patient demographics and comorbidity, medication, prothrombotic factors, and inflammation on graft failure.

In conclusion, the interrelationships between platelets, inflammation, and vascular disease weave a complex web. Future studies in patients undergoing CABG surgery should test more effective antiplatelet strategies than COX-1 inhibition and should identify promising targets for prevention of the vein graft disease that may culminate in occlusion.

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