The Problem of Persistent Platelet Activation in Acute Coronary Syndromes and Following Percutaneous Coronary Intervention

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ABSTRACT

Platelets play a central role in the atherosclerotic inflammatory response, thrombotic vascular occlusion, microembolization, vasoconstriction, and plaque progression. Persistent platelet activation poses a serious problem among patients with acute coronary syndromes (ACS) and those who have undergone percutaneous coronary intervention (PCI), placing them at risk for ischemic events and subacute stent thrombosis. Patients undergoing PCI are at risk for further ischemic events because of procedure-related platelet activation as well as the inherent persistent platelet hyperreactivity and enhanced thrombin generation associated with ACS. Persistent platelet activation following an acute coronary event and/or PCI supports incorporating antiplatelet strategies into the standard medical management of such patients. In this clinical setting, antiplatelet therapies are capable of improving outcomes. Aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibitors, the 3 major pharmacologic approaches to persistent platelet activation, target various levels of the hemostatic pathways and thrombus formation.

Key words: catheterization/diagnostic intervention<cardiac, cardiovasular, acute coronary syndromes <ischemic heart disease, myocardial infarction<ischemic heart disease, platelets, thrombosis/hypercoagulable states

Introduction

This brief review focuses on the role of platelets in atherosclerotic inflammatory response and persistent platelet activation in the setting of acute coronary syndrome (ACS), with a particular focus on patients undergoing percutaneous coronary intervention (PCI). The stage is set here for subsequent articles in the supplement that examine the contemporary use of platelet inhibitors in patients with ACS and those undergoing PCI, and remaining unmet needs in the field.

Atherosclerotic and Inflammatory Activities of Platelets

In addition to their well-described important role in thrombotic vascular occlusion, platelets also participate in microembolization and vasoconstriction, plaque progression, and systemic inflammatory responses associated with ACS.[1] Microembolization and resultant obstruction of the microvasculature are correlated with unfavorable long-term clinical prognosis.[2] Despite successful revascularization, microvascular obstruction, and platelet-induced vasospasm contribute significantly to inadequate perfusion and prolonged tissue ischemia in the myocardium. In addition, microembolization results in decreased myocardial contractility.[3] Platelets play a role in the initiation of atherosclerotic lesion formation, but contribute to plaque progression as well. Platelets within established plaques release a variety of growth factors (such as platelet-derived growth factor) and chemokines into the microenvironment; these activities can contribute to plaque progression.[1]

Inflammation is now recognized to have a central role in all stages of atherothrombosis, including early atherogenesis, lesion progression, and thrombotic complications

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of atherosclerosis.[4] A number of proinflammatory mediators are expressed by activated platelets, but CD40 ligand (CD40L) appears to be one of the most important platelet-derived proinflammatory mediators. Platelet CD40L interacts with CD40 on endothelial cells and leukocytes, triggering tissue factor and adhesion receptor expression and chemokine release. Platelets expressing CD40L thus induce inflammatory and procoagulant responses in vascular cells. Also, by promoting the release of matrix-degrading enzymes, CD40L might also contribute to plaque destabilization.[1,5]

Persistent Platelet Activation in the Setting of Acute Coronary Syndromes and Postpercutaneous Coronary Intervention

Standard pharmacological approaches used in patients who undergo PCI are intended to prevent post-PCI thrombotic complications by stabilizing atherosclerotic plaques at the target lesion and other remote atherosclerotic sites. Mechanical disruption of coronary plaques by denudation of the arterial endothelium and subsequent exposure to thrombogenic matrix proteins, in addition to underlying atherothrombotic disease, results in platelet activation during and following PCI. The PCI-mediated enhancement of vascular injury and platelet activation may be important causes of abrupt vessel closure, restenosis, and subacute stent thrombosis.[6–8]

Patients undergoing PCI are at risk for further ischemic events not only because procedure-related platelet activation occurs, but also due to the inherent persistent platelet hyperreactivity and enhanced thrombin generation associated with ACS.[9] For example, enhanced platelet reactivity in patients with stable coronary artery disease has been demonstrated via enhanced platelet surface expression of P-selectin in response to stimulation with low concentrations of agonists such as adenosine diphosphate (ADP) (Figure 1).[10] Importantly, the thrombolysis in myocardial infarction (TIMI) 12 trials suggested that activation of platelets continues long after clinical stabilization post-ACS. In that trial, significantly elevated platelet activation was demonstrated even 28 days following stabilization after an ACS (versus normal and patient controls; $p<0.05$ for both control groups).[11] High platelet reactivity in patients undergoing PCI has also been shown to be a risk factor for ischemic events following PCI. The platelet reactivity in patients and recurrent events (PREPARE) POST-STENTING study demonstrated higher posttreatment ADP-induced aggregation in patients who suffered ischemic events over a 6-month period compared with patients without ischemic events ($p = 0.02$) (Figure 2).[12]

A number of studies suggest that high platelet reactivity is associated with stent thrombosis (ST) in patients who have undergone PCI.[13,14] However, ST often presents as an acute myocardial infarction (MI), making it difficult to differentiate

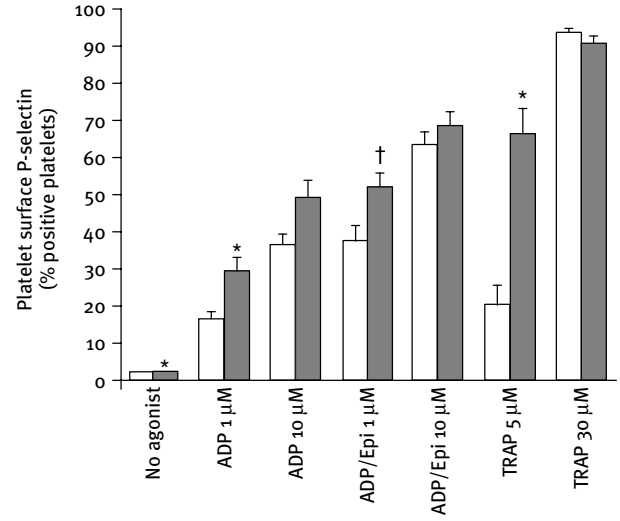

Figure 1: Platelet reactivity of patients with stable CAD (solid bars) compared with control subjects (open bars) as determined by platelet surface expression of P-selectin in response to exogenous agonist stimulation. $^{*}p<0.01$ $^{\dagger}p<0.05$. Reproduced with permission from Furman et al.[10]

whether the high platelet reactivity is the cause of ST rather than it being a manifestation of the ischemic event itself. A recent study found that patients who had undergone stenting and experienced ST had significantly higher ADP-induced P-selectin expression and platelet aggregation compared with patients who did not develop an ST. However, that same study demonstrated a similarly high platelet reactivity profile for patients with ST and patients with an acute ST stent thrombosis-segment elevation myocardial infarction (STEMI) treated with primary PCI.[15] Regardless of the remaining need for large prospective trials to determine causation of platelet hyperreactivity in the case of ST, these findings demonstrate further the high platelet reactivity that is characteristic of ACS and in patients who undergo PCI. The hyperthrombotic milieu observed post-PCI may persist over months or longer, and provides the rationale for short-

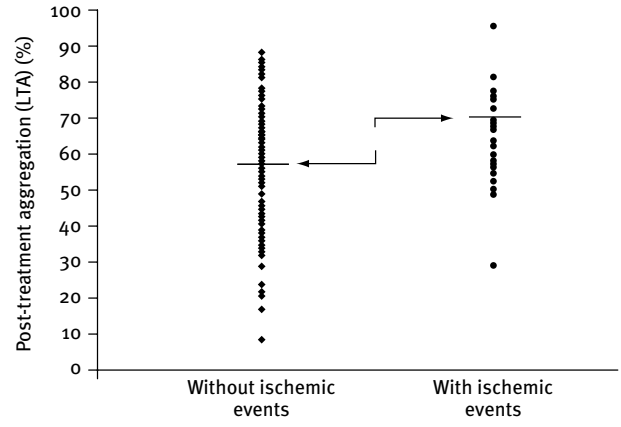

Figure 2: ADP-induced posttreatment platelet aggregation (20 µM) as measured by light transmittance aggregometry (LTA) in patients without ischemic events and with ischemic events. Reproduced with permission from Gurbel PA et al.[12]

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and long-term intervention with platelet inhibitors;[16] thus, antiplatelet therapy has become an integral component of patient care in the peri and postprocedure period.

Antiplatelet Interventions Used in Acute Coronary Syndromes

Pharmacologic antiplatelet interventions target various levels of the hemostatic pathways and thrombus formation (Figure 3).[17] The 3 current approaches to medical antiplatelet therapy used in patients with ACS are as follows:

- Aspirin (ASA): inhibits platelet activity via irreversible acetylation of cyclooxygenase 1, preventing the formation of thromboxane A_2–a potent mediator of platelet aggregation
- Thienopyridines: inhibit ADP-mediated stimulation of the $P2Y_{12}$ receptor resulting in inhibition of platelet activation and subsequently of platelet aggregation processes.
- Glycoprotein (GP) IIb/IIIa inhibitors: the GP IIb/IIIa receptor is a prothrombotic mediator of platelet activation and aggregation. Following activation, GP IIb/IIIa receptors are converted to a ligand-receptor conformation. Once activated, this platelet receptor binds the dimeric fibrinogen molecule and crosslinks adjacent platelets, thereby causing aggregation.

Conclusion

Platelets are central to the process of normal hemostasis. In the presence of coronary artery disease, they may form thrombotic vascular occlusion at ruptured coronary atherosclerotic plaque sites and also contribute substantially to impairment of coronary microcirculation and ongoing atherosclerotic inflammatory responses. The persistent effect of platelet hyperreactivity following an acute coronary event and/or PCI provides the rationale for integrating

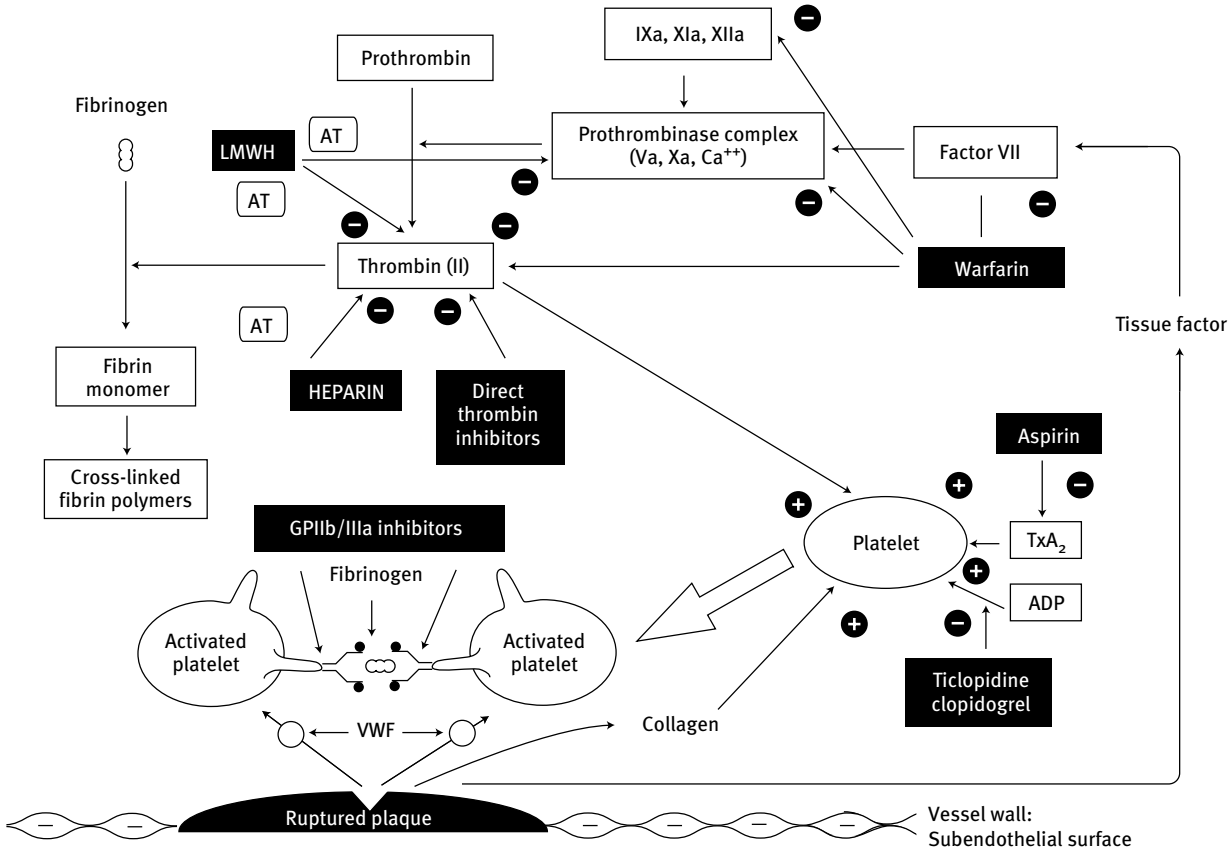

Figure 3: Interaction of platelets with components of thrombus formation and targets for pharmacological intervention. Reproduced with permission from Kristensen SD et al.[17]

antiplatelet strategies into the standard medical management of such patients; these therapies have substantially improved outcomes in certain patients in this setting. The three major approaches to antiplatelet therapy in patients with ACS have been briefly introduced here. In the next article, landmark trials are reviewed that established current antiplatelet approaches in patients with ACS and in those undergoing PCI.

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