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Cardiovascular Devices and Platelet Interactions
Understanding the Role of Injury, Flow, and Cellular Responses

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The objectives of the 2011 Platelet Colloquium were to gain a better understanding of the role of platelets and inflammatory cells in the response to cardiovascular device–associated injury; to describe the relationship between cardiac devices, shear stress, and alterations in platelet biology and function; and to review evidence derived from in vitro, in vivo, and clinical investigations supporting therapies to modify platelet and inflammatory cell–associated responses to device-related injury.

Accordingly, this review summarizes the evidence for translating basic scientific concepts underlying circulatory and device-associated vascular injury to the clinical development and use of cardiac devices, supplemented by findings from the literature. Insights for platelet receptor activation, inflammatory cell biology, endothelial dysregulation, and the effects of biomechanical stress on coagulation and hemostatic proteins were examined to better determine the pathobiology, incidence, and possible prevention of adverse events in patients receiving cardiac devices.

Shear Stress and Platelet Activation

Hemodynamics play a key role in thrombus formation. Pathophysiological shear stress induces activation of platelets and the endothelium, increases platelet–leukocyte interactions, and promotes thrombin generation. The initial tethering of rolling activated platelets, subsequent stable adhesion, and aggregation each are influenced by shear stress on the vessel wall, which can range from 11.4 to 30.4 dyne/cm² in large arteries and up to 380 dyne/cm² at critical areas of arterial stenosis. Along a diseased vessel, shear forces will vary dramatically within short distances, increasing as the lumen narrows and then decreasing in the poststenotic vascular segment.

Several platelet membrane proteins serve as mechanosensors, most notably glycoprotein (GP) Ib and its ligand, von Willebrand factor (vWF). VWF circulates as highly adhesive multimers (ultralarge vWF) that are cleaved by a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13 (ADAMTS-13). Depletion or accumulation of ultralarge vWF, as a consequence of inappropriate ADAMTS-13 proteolysis, results in pathological bleeding (as in some patients with type 2A von Willebrand disease) or microvascular thrombosis (as with thrombotic thrombocytopenic purpura), respectively.

Shearing forces regulate vWF multimer size by unfolding a Tyr1605–Met1606 bond within the vWF-A2 domain such that it becomes a substrate for ADAMTS-13 cleavage. Platelet GP Ib responds to higher shear with increased vWF binding and intracellular signaling, in part by generating a calcium flux that together with phosphoinositide 3-kinase triggers integrin αIIbβ3 activation. These signals convert transient platelet surface interactions into stable integrin–mediated adhesion. During shear-induced platelet activation in vitro, released adenosine diphosphate (ADP) plays a fundamental role in this important process.

Temporal shear gradients promote cooperative signaling between the purinergic P2Y1 receptor and integrin αIIbβ3, which in turn contributes to the development of P2Y12-dependent stable platelet thrombi. Shear stress dissociates integrin αIIbβ3–cytoskeletal protein interactions, including associations with α-actin and myosin heavy chains, although the consequences of this disruption are unknown.

Several factors stabilize formed platelet aggregates. The intercellular space between aggregating platelets provides a

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protective environment for accumulation of ADP, thrombin,
thromboxane A2, Gas-6, and exodomains of platelet sur-
face proteins such as GP Ib, CD62, and soluble CD40
ligand.13 The contributions of the \( \alpha_{IIb} \beta_3 \) and
\( \alpha_{IIb} \beta_1 \), P2Y1, P2Y12, and integrins are also critical to
development of stable thrombi.14–17 Accordingly, agents targeting these latter re-
ceptors can reduce existing thrombus burden,18,19 although
increased intracoronary dose levels may be necessary to
dissolve rather than prevent thrombus.20

The effects of shear on platelets might extend beyond acute
activation and thrombosis. Platelets have played a role in
atherosclerosis initiation and/or progression in animal mod-
els, although the exact role of platelet activation is still
uncertain.21,22 Inhibition of platelet activation, vWF defi-
ciency, GP Ib blockade, and \( \alpha_{IIb} \beta_3 \) integrins all have shown
protective effects against atherogenesis in mice.23–25 In a
study of recombinant platelet GP Ib as the targeting entity on
lipid-shelled decafluorobutane microbubbles to detect “acti-
vated” vWF and other GP Ib ligands, Lindner et al26 detected
microbubble accumulation along thrombi formed by ex vivo
perfusion of human blood over a collagen surface and along
atherosclerotic vessels. In atherosclerotic mice, signal
strength likewise was greatest in areas with severe athero-
sclerotic lesions and in regions associated with platelet
accumulation.

Oxidation of vWF by oxidants derived from inflammatory
leukocytes can render vWF more stable, with enhanced
platelet binding and aggregatory effects.27 The potential
combined effects of shear and inflammation on vWF-platelet
binding highlights the complex interplay among shear stress,
inflammation, and platelet–leukocyte activation (Figure 1).
Other shear/platelet/inflammatory interactions are undoubt-
edly at play at the site of atherosclerotic lesions, such as the
formation of platelet–leukocyte heterotypic aggregates in-
duced by shear-mediated P-selectin induction in platelets.28
Other effects of shear on vascular inflammation are further
examined elsewhere.29

\begin{figure}
\centering
\includegraphics[width=\textwidth]{f1.png}
\caption{Complex interplay among shear stress, inflammation, and platelet–leukocyte activation. vWF indicates von Willebrand factor; RBC, red blood cell; PSGL, P-selectin glycoprotein ligand; GP, glycoprotein; PKC, protein kinase C; TGF, transforming growth factor; and ADP, adenosine diphosphate.}
\end{figure}

In Vivo and In Vitro Modeling of Platelet Function Under Shear

Most of the classic methods for testing platelet function do
not accurately reflect in vivo events occurring along vascular
surfaces in the presence of flowing blood. Even putative
markers for “in vivo platelet activation”—platelet micropar-
ticles, \( \beta \)-thromboglobulin, and thromboxane—exhibit poor
reproducibility.30 Tests of platelet “activatability,” such as
classic aggregation testing, flow cytometry, VerifyNow
point-of-care testing, and the MultiPlate system, rely on
low-shear settings that may not accurately mimic the high-
shear environment present within diseased blood vessels.
Several strategies to model and monitor platelets under more
physiological conditions, including animal models, imaging
in humans, and in vitro flow are now being used, a selection
of which is summarized in Table 1.

Newer technologies permit real-time measurement of in
vivo thrombus development in animal models, by means of a
wide-field fluorescence microscope fitted with a confocal
head.31 Using these technologies, several hallmarks of plate-
let activation have been observed (Table 2). In one instance,
pretreatment of mice with 1.25 \( \mu g/kg \) aspirin by mouth
1 hour before laser injury of mouse cremaster muscle arterioles
did not affect platelet accumulation (thrombus volume) but
reduced activation of integrin \( \alpha_{IIb} \beta_3 \) by 67% as assessed by
high-speed, 2-color confocal microscopy.32 Such technolo-
gies may further our understanding of platelet activation in
vivo and thus allow the design of more effective inhibitors.

Strategies for monitoring interactions between shear and
antiplatelet drug effects have been developed for humans. For
example, Yong et al33 obtained blood from the coronary
arteries proximal and distal to coronary lesions and from the
coronary sinus in patients with stable coronary artery disease
taking both aspirin and clopidogrel. After estimating the shear
stress from 3-dimensional coronary angiographic images of
these arteries, they assessed the effects of stenosis severity
and shear stress on in vivo activation of platelets and
monocytes. They found increased platelet P-selectin expres-
sion, platelet–monocyte aggregation, and monocyte CD11b expression, but integrin αIIbβ3 activation and soluble P-selectin did not correlate with stenosis severity and shear stress. Shear-related intracoronary platelet and monocyte activation might represent a therapeutic target distinct from conventional antiplatelet agents.

**Modeling Platelet-Device Interactions**
Thrombotic complications with cardiovascular devices remain a critical limitation to their long-term use. Device-induced shear forces can enhance hemostatic response through chronic activation of platelets, with a known dose-time response in terms of accumulated stress.34 Because of the relative infrequency of thrombosis with current models of stents, however, demonstrating its reduction in clinical trials of newer stent platforms will probably require tens of thousands of patients.

**Table 2. Hallmarks of Platelet Activation Seen With New In Vivo Technologies**

<table>
<thead>
<tr>
<th>Hallmark</th>
<th>Physiology</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>αIIbβ3 integrin increase and activation</td>
<td>Stable aggregation</td>
<td>Antibody to αIIb or activated ligand bound to integrin</td>
</tr>
</tbody>
</table>
| Dense granule secretion          | ADP, serotonin release for amplification | Lumiaggregometry or 
                                                                 | 14C]SHT release |
| α-Granule secretion              | P-selectin for cell interaction     | Antibody to P-selectin                            |
|                                   | Procoagulants (V)                    | Prothrombin activation                           |
| Phosphatidylserine expression     | Procoagulant surface                 | Annexin/Diannexin                                |
| Platelet–leukocyte interaction   | Inflammatory/thrombotic signaling    | Genetically labeled platelets/leukocytes and their antibodies |
| Receptor shedding                 | Downregulation?                     | Antibody                                          |

ADP indicates adenosine diphosphate.

Alternatively, in vitro modeling techniques for testing device-mediated thrombogenicity, coupled with virtual design modifications in an iterative approach, could be incorporated during device research and development. Such a method would optimize the thrombogenic performance of the device before prototypes are tested in costly preclinical and clinical trials.

Rather than testing device-mediated thrombogenicity in clinical trials or animal models, an attractive alternative strategy might be to harness in vitro modeling techniques that could be incorporated during device research and development. Such a method would use virtual design modifications in an iterative approach to optimize the thrombogenic performance of the device before prototypes are built and tested in costly preclinical and clinical trials.

A recent study used in vitro flow-chamber studies to compare platelet aggregation after exposure to drug-eluting stents (DES) and bare metal stents (BMS) with variable strut thickness. The thin-polymer/thin-strut DES elicited less platelet activation and aggregation than did the thick-strut DES; more important, the thin-polymer/thin-strut DES in this model provoked less platelet activation/aggregation than did the BMS platforms.35 Such in vitro modeling allows rational development and examination of small changes in device designs as a method for guiding future trial designs.

Another example of effective in vitro modeling uses a real-time chromogenic assay27 to measure thrombin formation, which can be applied to understand the impact of devices on the thrombogenicity of flowing blood. Thrombin formation is monitored as blood flows past mechanical devices, and the extent of thrombin generation relates directly to the platelet activation and aggregation induced.36–38 Chromogenic monitoring of thrombin generation can be coupled with a novel hemodynamic shearing device (HSD) to expose platelets to dynamic shear-stress waveforms as extracted from advanced numeric simulations of blood flow through the device. This shearing device can allow comprehensive...
evaluation of the thrombogenic potential of devices as a potential surrogate for initial animal or human testing (Figure 2). This system can identify “hot spot” regions within the device during distinct flow phases and compute flow trajectories and stress load histories within these regions. Designs can then be iteratively modified to reduce thrombogenic potential computed in the virtual domain and the resultant stress-loading waveforms programmed and tested in the HSD. This system has been termed the “device thrombogenicity emulator” (DTE). Although primarily used to study mechanical circulatory support devices and bileaflet mechanical heart valves, in vitro assessment of hemodynamic shearing forces and subsequent platelet activation might be an efficient means of making iterative changes in other potentially thrombogenic cardiac and arterial devices, including stents. The HSD can study the interaction between flowing platelets and cell-cultured endothelium. The system is operated under emulated shear stress loading conditions extracted from numeric simulations of blood flow in various device configurations. In this manner, the HSD could allow expeditious assessment of iterative device designs with respect to platelet activation and thrombogenicity.

Role of Platelet Biology in Device-Induced Injury

In addition to mediating acute arterial thrombosis, platelets play a critical role in the response to and recovery from vascular injury. Activated platelets interact with leukocytes after device deployment and promote the recruitment of leukocytes to inflamed endothelium. Platelets contain variable levels of mRNAs, premRNAs, and microRNAs and a repertoire of translational pathways for posttranscriptional synthesis of new proteins. Both genetic and environmental factors influence the expression patterns of transcripts and their corresponding protein products. For example, the differential expression of several inflammatory transcripts correlates with body mass index and cardiovascular disease. Analyzing acute and prolonged changes in the platelet transcriptome and proteome might prove fruitful in identifying causes for differences in outcomes of device-mediated injury.

Experimental models of restenosis have shown direct correlations between the frequency and severity of cyclic flow variations, platelet aggregation, and neointimal proliferation. Moreover, in animal models, administration of agents that block the ADP, thromboxane A₂, and serotonin pathways and agents that inhibit platelet-monocyte interactions results in significantly larger residual luminal areas. In humans, platelet reactivity measured before percutaneous coronary intervention (PCI) has been linked to repeat revascularization at 90 days and target-vessel revascularization at 7 months.

Despite the solid mechanistic underpinning for antiplatelet agents in modulating the response to vascular injury after
Histopathologic Insights Into Acute and Delayed Healing Responses After BMS/DES Implantation

Although platelets have played a critical role in responses to vascular injury in several animal models, available antiplatelet therapies generally have failed to show a favorable effect on restenosis in clinical trials. This does not mean that platelet-mediated growth factor and inflammatory responses do not play large roles in the processes of arterial injury and repair. Both balloon dilatation and stenting result in endothelial denudation, whereby adhesion molecules such as P-selectin mediate platelet-leukocyte-endothelial cell interactions. These interactions spur platelets to release cytokines and growth factors that mediate smooth muscle cell migration and proliferation.73–75

The mechanisms for development of intimal hyperplasia can differ after angioplasty versus stenting. For example, unlike angioplasty, which initiates early neutrophil recruitment, stenting tends to result in prolonged macrophage recruitment.76 Nonetheless, the downstream pathways involved in arterial injury all initiate the cell cycle regulated by cycling-dependent kinases. Agents that inhibit these kinases, such as rapamycin, are extremely effective in inhibiting restenosis, especially when delivered locally. This phenomenon highlights the importance of common molecular signaling pathways that initiate the process of intimal formation.

Technical improvements in PCI and stents have reduced restenosis rates from 30% in the 1980s to <10% today. The introduction of BMS in the 1990s represented a significant advance, with additional refinement in the 2000s through the debut of DES. Even within the DES category, designs have continued to evolve in an effort to optimize outcomes. Stent strut widths, for example, have decreased from 97 to 140 μm with the first generation of devices (Cypher, Taxus) to 81 to 91 μm with the second (Endeavor, Xience). Thinner strut struts may be associated with improved clinical outcomes, but further study is needed for clarification.58–79

The mechanisms of late and very late stent thrombosis (LST) are unknown. Clinical trials using prasugrel or ticagrelor clearly demonstrate a role of P2Y12 receptors in LST.80,81 In analyses of autopsy and clinical registry data, DES have been associated with delayed coronary arterial healing, as evidenced by persistent fibrin deposition and reduced endothelialization, and an increased risk of LST compared with BMS.82,83 In 1 case-control analysis of data from 62 lesions in the CVPath Institute’s registry, endothelialization was the best independent predictor of thrombosis >30 days after stenting, which in turn was best correlated with the ratio of uncovered to total stent struts per section (odds ratio for thrombus in a stent with a >30% ratio of uncovered to total stent struts/section, 9.0; 95% confidence interval, 3.5–22).84

One potential mechanism for LST, at least among some first-generation stents, relates to hypersensitivity reactions85 that appeared to be limited to sirolimus-eluting devices.85 However, stent malapposition secondary to excessive fibrin deposition appeared to be an exclusive characteristic of paclitaxel-eluting stents in analysis of 230 lesions from the CVPath registry.86 Another analysis of 51 patients from the same registry implicated stenting for acute MI in development of LST.87 Compared with patients who had stable
angina with thick-cap fibroatheromas, those with an MI culprit site had significantly smaller neointimal thickness (0.04 versus 0.11 mm) and greater proportions of uncovered struts (49% versus 9%), struts with fibrin deposition (63% versus 36%), and struts with inflammation (35% versus 17%; all \( P \leq 0.01 \)).

These findings emphasize the importance of plaque morphology to arterial responses after DES implantation.

Neoatherosclerotic changes developing within the neointima after stenting have also been proposed as a mechanism for LST. Atherosclerosis develops earlier and more often within the neointima among patients receiving DES versus BMS. In patients undergoing follow-up intravascular imaging at least 20 months after DES placement, features consistent with high-risk plaques, such as rupture and thrombi within the neointima, have been noted. This unstable neoatherosclerosis in DES-treated patients probably contributes to late thrombotic events.

The number of uncovered struts might serve as a surrogate measure of epithelialization/neointimal coverage after stenting and thus might inform the duration of antiplatelet therapy. Optical coherence tomography (OCT) has been proposed as a noninvasive method of assessing this surrogate. In a study of 243 patients undergoing DES implantation, neointimal hyperplasia morphology on OCT correlated moderately with simultaneous intravascular ultrasound findings obtained a mean 12 months after stenting, but assessments differed in 31% of lesions. Another analysis of 622 OCT-histology–matched samples from 84 stents of 4 types showed good correlations between methods in neointimal area, luminal area, and neointimal thickness. Overall, the proportions of uncovered struts identified by OCT and histology were similar, but estimations varied significantly between methods at neointimal thicknesses of 20 to 80 \( \mu m \). Whether OCT-determined strut coverage can actually predict clinical outcomes remains to be determined.

Modeling in large animals and humans has correlated shear stress with neointimal proliferation in stents. Human studies comparing BMS and DES identified shear stress as an independent predictor of neointimal thickness, with sirolimus-eluting stents (but not paclitaxel-eluting stents) reducing the effect of shear stress on neointimal proliferation.

Inflammatory and platelet activation reactions, including stent thrombosis, might be a lesser problem with newer DES. In a flow-loop model assessing in vitro thrombogenicity of DES, drug/polymer coatings did not enhance thrombogenicity compared with their BMS counterparts, although stent positioning and design were determinants of stent thrombogenicity. More recent randomized trials also have failed to show a clear increase in LST risk with DES versus BMS. For example, the Efficacy of XiencePromus versus Cypher in rEducing Late Loss after stENting (EXCELLENT) trial comparing Xience and BMS suggests that second-generation DES might carry an even lower 1-year rate of LST than do BMS. Of note, this trial was a noninferiority study based on late loss; it was powered to examine “hard” end points such as stent thrombosis or MI. Thus, definitive conclusions cannot be made about the safety of one device versus another at present. Biocompatible polymers, and disappearing polymers/stents, might minimize some of the concerns regarding pathological platelet activation and inflammation.

Summary
Shear influences platelet adhesion and activation through mechanisms that include altering vWF binding and \( \alpha_{IIb/\beta_3} \) purinergic signaling interactions. Shear can potentially promote inflammation and atherogenesis through platelet-mediated processes. New methods to study platelet function under shear conditions and in more physiological contexts should be incorporated to guide the design of future devices and drug therapies. Some of these methods include in vivo imaging, in vitro flow models, and in vitro modeling/computer-assisted iterative device design.

Improving currently used antiplatelet agents is not the sole answer for reducing vascular injury after PCI. Cilostazol and statins are promising examples of agents that have effects beyond inhibition of platelet activation. In addition, LST, which has been associated with both stent design and pathological changes (such as endothelialization and neoatherosclerosis within the neointima), is becoming a less critical issue with DES because of the use of DAPT and newer stent designs.

Conclusions
Our knowledge regarding interactions among platelets, vascular flow conditions, and cardiovascular device characteristics continues to evolve. Simultaneously, we are better appreciating the role of inflammatory cells in the response to cardiac device–associated injury. Novel in vitro and in vivo techniques now permit accurate assessment of the thrombogenicity of new device designs and might aid in development of therapeutic targets distinct from conventional antiplatelet agents. By focusing on the mechanistic aspects of cardiac devices and the vasculature, and on the inflammatory response, the goal of translating promising interventions to optimal patient care can be achieved more rapidly and efficiently.

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References


44. Rowley JW, Oler A, Tolley ND, Hunter B, Low EN, Nix DA, Yost CC, Rowley et al. Cardiovascular Devices and Platelets


52. Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Sal-


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Appendix. Participants in the 2011 *Platelet Colloquium*

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