

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.¹ 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.²

Several platelet membrane proteins serve as mechanosensors, most notably glycoprotein (GP) Ib and its ligand, von Willebrand factor (vWF).³ 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.^{3–6} Platelet GP Ib responds to higher shear with increased vWF binding and intracellular signaling, in part by generating a calcium flux⁷ that together with phosphoinositide 3-kinase⁸ triggers integrin $\alpha_{IIb}\beta_3$ activation.^{7,9} 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 $\alpha_{IIb}\beta_3$,^{10,11} which in turn contributes to the development of P2Y₁₂-dependent stable platelet thrombi.¹¹ Shear stress dissociates integrin $\alpha_{IIb}\beta_3$ -cytoskeletal protein interactions, including associations with α -actin and myosin heavy chains,¹² 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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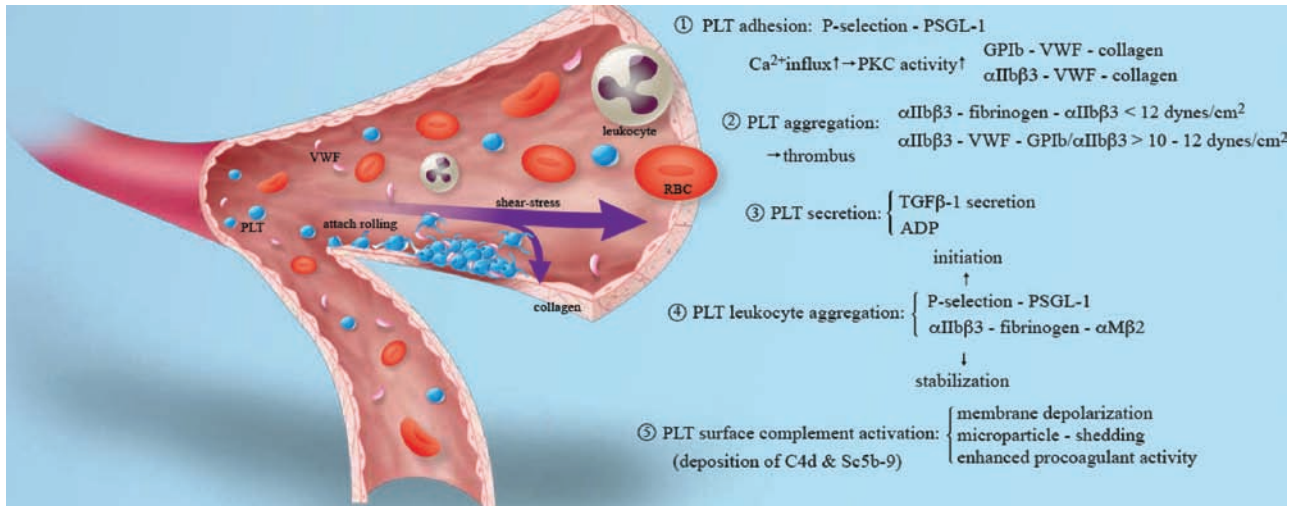


Figure 1. Complex interplay among shear stress, inflammation, and platelet–leukocyte activation. vWF indicates von Willebrand factor; RBC, red blood cell; PSGL, P-selectin glycoprotein ligand; GP, glycoprotein; PKC, protein kinase C; TGF, transforming growth factor; and ADP, adenosine diphosphate.

protective environment for accumulation of ADP, thrombin, thromboxane A₂, Gas-6, and exodomains of platelet surface proteins such as GP Ib, CD62, and soluble CD40 ligand.¹³ The contributions of the $\alpha_{IIb}\beta_3$, P2Y₁, P2Y₁₂, and $\alpha_{IIb}\beta_3$ integrins are also critical to development of stable thrombi.^{14–17} Accordingly, agents targeting these latter receptors 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 models, although the exact role of platelet activation is still uncertain.^{21,22} Inhibition of platelet activation, vWF deficiency, GP Ib blockade, and $\alpha_{IIb}\beta_3$ deficiency 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 “activated” 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 atherosclerotic 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 affects.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 undoubtedly at play at the site of atherosclerotic lesions, such as the formation of platelet–leukocyte heterotypic aggregates induced by shear-mediated P-selectin induction in platelets.²⁸ Other effects of shear on vascular inflammation are further examined elsewhere.²⁹

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 microparticles, β -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 platelet activation have been observed (Table 2). In one instance, pretreatment of mice with 1.25 μ 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 technologies 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-

Table 1. Advantages and Disadvantages of Selected In Vitro and In Vivo Methods Used to Measure Platelet Activation*

Method	Advantages	Disadvantages
Confocal imaging in mice of in vivo platelet activation and thrombus formation	Genetically manipulated, environmentally controlled, lower cost, can visualize multiple parameters at once in real time in physiological context	Species differences in cell size, molecular signatures, vessel size, shear; not amenable to device testing
Large-animal studies	Environmentally controlled, more similar cell sizes and shears (animal-dependent), can study devices/drugs in physiological context	Species differences molecular signatures, higher cost, limited availability
Contrast ultrasound with microbubbles targeting platelet ligands and activation markers	Potential translation to humans, can study devices/drugs in physiological context	Higher cost, limited availability
Indices of platelets (from lesion) coupled with 3-dimensional coronary angiography	In humans, can study devices/drugs in physiological context	Higher cost, indirect measurement after blood draw, limited availability
In vitro chromogenic assays of thrombin formation coupled with hemodynamic shearing device	Low cost, wide availability, no requirement for humans or animals, better than static assays, can perform real-time measurements, rapid	Cannot study in physiological context
In vitro flow chamber studies	Low cost, wide availability, no requirement for humans or animals, can test many variables from single sample, better than static assays, rapid	Cannot study in physiological context

*Methods discussed in the text; not meant to be comprehensive.

sion, platelet-monocyte aggregation, and monocyte CD11b expression, but integrin $\alpha_{IIb}\beta_3$ 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

Hallmark	Physiology	Marker
$\alpha_{IIb}\beta_3$ Integrin increase and activation	Stable aggregation	Antibody to α_{IIb} or activated ligand bound to integrin
Dense granule secretion	ADP, serotonin release for amplification	Lumiaggregometry or ^{14}C]5HT release
α -Granule secretion	P-selectin for cell interaction	Antibody to P-selectin
	Procoagulants (V)	Prothrombin activation
	Anti/angiogenic factors	PF4
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

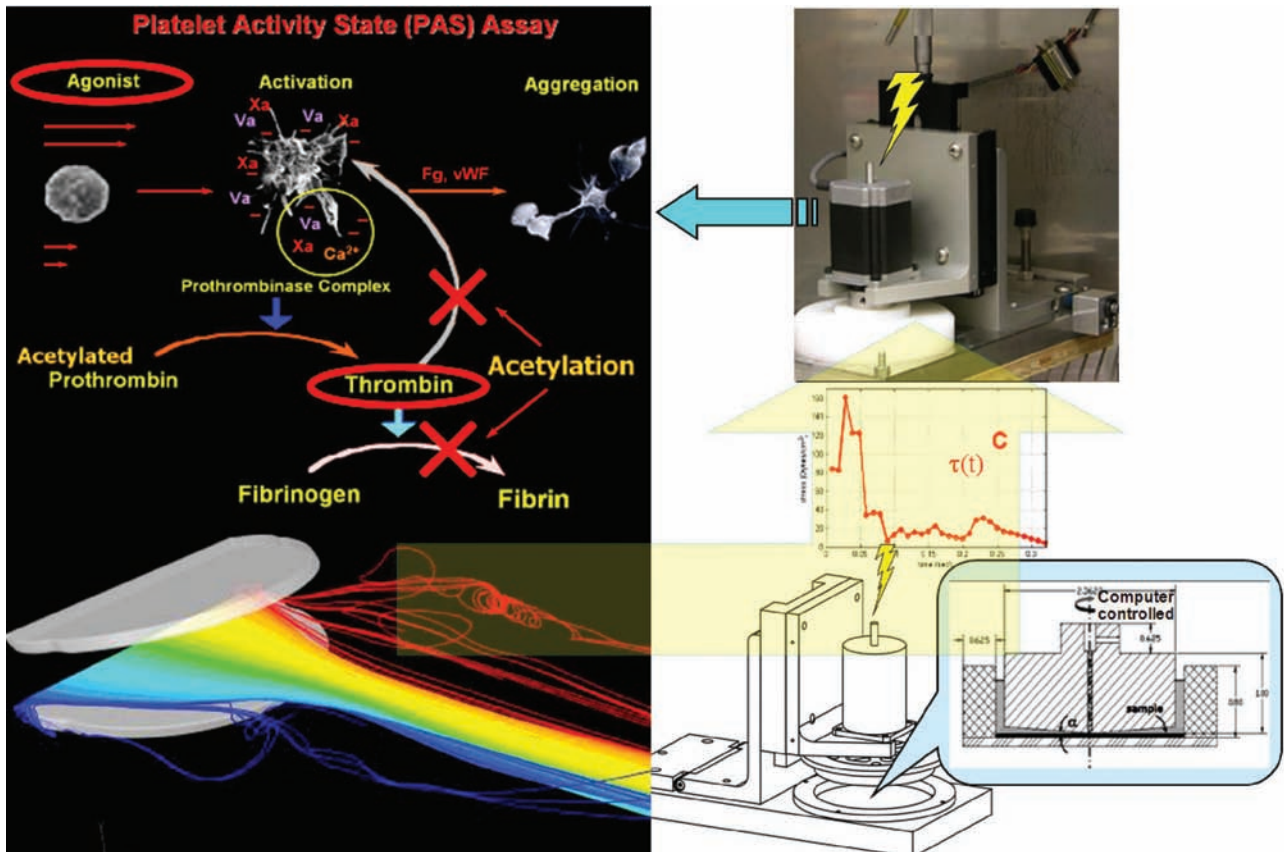


Figure 2. Device thrombogenicity emulator. “Hot spot” trajectories from numeric simulations (shown, blood flow through a bileaflet mechanical heart valve, **top**) are translated into shear stress–loading waveforms $\tau(t)$. These waveforms are then programmed into the hemodynamic shearing device (**bottom left**), platelets are repeatedly exposed to them, and the resultant activity is measured using a platelet activity state assay (**bottom right**). Adapted from Bluestein et al,³⁹ with permission. VWF indicates von Willebrand factor.

evaluation of the thrombogenic potential of devices as a potential surrogate for initial animal or human testing (Figure 2).³⁹ 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,^{40,41} 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.⁴² 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.³⁵

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 deployment⁴³ 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.^{44–46} 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.⁴⁷ 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.^{48–50} Moreover, in animal models, administration of agents that block the ADP, thromboxane A₂, and serotonin pathways⁴⁹ and agents that inhibit platelet-monocyte interactions⁵⁰ 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 days⁵¹ and target-vessel revascularization at 7 months.⁵²

Despite the solid mechanistic underpinning for antiplatelet agents in modulating the response to vascular injury after

PCI, large clinical investigations have yielded mostly disappointing results in terms of clinical outcomes.^{53–55} Even abciximab, which substantially reduced the incidence of target vessel revascularization in 2 pivotal trials,^{56,57} has failed to show significant benefit in reducing restenosis.^{58–60} Clearly, inhibition of platelet aggregation is not the sole answer to improving outcomes after vascular trauma.

Several studies have investigated the ability of cilostazol, a phosphodiesterase III inhibitor approved in the United States for treatment of intermittent claudication, to limit neointimal proliferation after stenting. A recent meta-analysis of 10 randomized trials (n=2809 patients overall) reported a significant, 48% decrease in angiographic restenosis when cilostazol was added to aspirin and thienopyridine therapy, without major differences between BMS or DES cohorts.⁶¹ Target lesion revascularization was reduced by 62%, but subacute stent thrombosis and major bleeding did not differ significantly. An initial randomized trial of a new, cilostazol-eluting stent reported significantly reduced in-stent late loss and restenosis versus a paclitaxel-eluting stent, with no stent thrombosis or myocardial infarction (MI) in any of the 111 patients at 8 months.⁶² This technology might represent a promising new type of DES system.

Alternatively, based on the mechanistic role of inflammation in vascular injury,⁶³ several investigations have centered on the antiplatelet and anti-inflammatory effects of statins as a means to facilitate recovery from vascular injury.^{64–66} Plasma levels of soluble CD40 ligand and prothrombin fragment F1.2 were significantly reduced among hypercholesterolemic patients who received atorvastatin for 3 days (n=15) versus diet (n=15), and atorvastatin was associated with a dose-dependent, significant decrease in platelet CD40 ligand expression in vitro among both the hypercholesterolemic patients and 20 healthy control subjects.⁶⁴ Previous animal models have shown atheroma formation and regression to be CD40 ligand-dependent.⁶⁷ These mechanistic data may partly explain the findings of the REVERSIng atherosclerosis with Aggressive Lipid lowering (REVERSAL) trial and A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound (ASTEROID), in which patients receiving intensive statin therapy (atorvastatin 80 mg or rosuvastatin 40 mg daily, respectively) showed dose-dependent, significant decreases in atheroma volume on intravascular ultrasonography.^{65,66}

Recent studies examining high-dose statin therapy given 24 hours before PCI suggest that short-term 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibition might reduce ischemic events.^{68,69} The mechanisms responsible are unknown but are probably not mediated primarily by reduced low-density lipoprotein C levels. The early beneficial effects of statins on ischemic events might reflect antiplatelet and/or anti-inflammatory properties. Statin therapy has been associated with lower urinary thromboxane levels,⁷⁰ a marker of activated circulating platelets, and reduced ex vivo shear-induced platelet activation.⁷¹ However, not all studies have found an effect of statins on platelet function.⁷²

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 stent struts may be associated with improved clinical outcomes, but further study is needed for clarification.^{58,77–79}

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 $P \leq 0.01$).⁸⁷ 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.⁸⁸ 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.⁸⁸ 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.⁸⁹ 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.⁹⁰ 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 μm . Whether OCT-determined strut coverage can actually predict clinical outcomes remains to be determined.

Modeling in large animals⁹¹ and humans⁹² 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,⁹³ 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.⁹⁴ 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.³⁵ More recent randomized trials also have failed to show a clear increase in LST risk with DES versus BMS. For example, the Efficacy of Xience/Promus 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.⁹⁵ Of note, this trial was a noninferiority study based on late loss; it was unpowered 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.^{95,96}

Summary

Shear influences platelet adhesion and activation through mechanisms that include altering vWF binding and $\alpha_{\text{IIb}}\beta_3$ /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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KEY WORDS: platelets ■ shear ■ stents ■ blood flow

Appendix. Participants in the 2011 *Platelet Colloquium*

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