Beyond Thrombosis

The Versatile Platelet in Critical Illness

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Sepsis, acute lung injury, and ARDS contribute substantially to the expanding burden of critical illness within our ICUs. Each of these processes is characterized by a myriad of injurious events, including apoptosis, microvascular dysfunction, abnormal coagulation, and dysregulated host immunity. Only recently have platelets—long considered merely effectors of thrombosis—been implicated in inflammatory conditions and the pathobiology of these disease processes. A growing body of evidence suggests a prominent role for maladaptive platelet activation and aggregation during sepsis and ARDS and has begun to underscore the pluripotential influence of platelets on outcomes in critical illness. Not only do platelets enhance vascular injury through thrombotic mechanisms but also appear to help orchestrate pathologic immune responses and are pivotal players in facilitating leukocyte recruitment to vulnerable tissue. These events contribute to the organ damage and poor patient outcomes that still plague the care of these high-risk individuals. An understanding of the role of platelets in critical illness also highlights the potential for both the development of risk stratification schema and the use of novel, targeted therapies that might alter the natural history of sepsis, acute lung injury, and ARDS. Future studies of adenosine, platelet polyphosphates, and the platelet transcriptome/proteome also should add considerably to our ability to unravel the mysteries of the versatile platelet. *CHEST 2011; 139(3):658–668*

Abbreviations: ADP = adenosine diphosphate; ALI = acute lung injury; CRP = C-reactive protein; GP IIb/IIIa = glycoprotein IIb/IIIa; PCI = percutaneous coronary intervention; vWF = von Willebrand factor

Sepsis, acute lung injury (ALI), and ARDS all contribute substantially to the expanding burden of critical illness within the United States. Epidemiologic estimates suggest an incidence of 200,000 patients annually for ALI/ARDS,[1,2] with a comparably large and growing incidence of sepsis.[3] The morbidity and mortality of these disease processes likewise are staggering. In-hospital death rates range from 26% to 38% in studies of ARDS,[1,2] whereas sepsis kills nearly one-half of those severely affected.[4] For patients who ultimately survive their initial hospitalization, quality of life often is dramatically reduced, and the economic impact is considerable. Sepsis, for instance, contributes nearly $17 billion toward the burgeoning costs of US critical care delivery.[5]

From a pathophysiologic perspective, sepsis, ALI, and ARDS are all characterized by abnormally enhanced coagulation, dysregulated and often injurious host immunity, microvascular dysfunction, and tissue necrosis. Increasing evidence suggests that hematologic derangements are associated with and may be important contributors to disease severity, largely influenced by alterations in platelet and leukocyte function.[6] Although platelet-mediated thrombosis has been implicated in their pathobiology, a host of other platelet-associated effects can influence their natural history. Understanding the pluripotential impact of platelets in immunopathology and their specific role in the development and progression of

critical illness is vitally important to those clinicians and investigators who hope to improve the care of these high-risk patients.

Overview of Platelet Structure and Function

Platelets are anucleate cells of myeloid origin that continuously flow in a quiescent state throughout the human vasculature.[7] Derived from megakaryocytes, the circulating platelet readies itself to perform a myriad of hemostatic, inflammatory, and reparative tasks once activated.[8] Under conditions of heightened demand, platelet production can increase by as much as 20-fold. When summoned by tissue injury and inflammation, this amplified platelet offensive can then exert its influence on a variety of other cells directly or through the release of highly potent intracellular constituents.

Platelet recruitment and adhesion are orchestrated by a number of specialized chemokines, adhesion molecules, and receptors. In particular, platelets express cell surface receptors called integrins. Integrins make up a large family of receptors that are constitutively expressed on the surface of many cells and whose job it is to facilitate both cell-to-cell and cell-to-extracellular matrix interactions.[9] Perhaps the most well known and most abundant platelet integrin is the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor. Following cellular activation, GP IIb/IIIa binds fibrinogen, fibrin, and other ligands, mediating adhesive events and stimulating platelet aggregation. Other integrins play key roles in adhesion, aggregation, thrombus formation, and vascular repair.

In addition to the integrins, there are a number of G-protein-coupled receptors present on the platelet surface that promote platelet activation, changes in platelet rheology, and enhanced aggregation. Protease-activated receptor 1, for example, plays a pivotal role in the activation of platelets.[9] Thromboxane A_2 induces aggregation and vascular smooth muscle contraction. Stimulation of adenosine diphosphate (ADP) receptors on the platelet surface results in alterations in platelet shape and supports further platelet aggregation.

The metabolically primed armamentarium of the platelet extends beyond these cell surface receptors, however. Platelets also express and release a variety of adhesion molecules, mitogenic factors, and vasoactive compounds, all of which play key roles in modulating endothelial function, aggregation, and cellular interactions. These compounds include cytoplasmic substances such as serotonin, epinephrine, norepinephrine, nitric oxide, vascular endothelial growth factor, and transforming growth factor β[8]; the selectins, which interact with cell surface glycoconjugates to mediate adhesion and cellular communication[10]; and mitochondrial lysosomes, which store and release potent glycosidases, proteases, and cationic proteins.[11] Platelets also contain α granules, which release important contributors to coagulation,[9] and dense granules, which release nonprotein molecules, including ADP, calcium, and serotonin, that modulate inflammatory and thrombotic processes (Table 1).[11]

It is well known that platelets are the primary effector cells of hemostasis, and their roles in both thrombosis and vascular repair have been well established. There are four main phases governing platelet function: (1) activation, (2) adhesion, (3) aggregation, and (4) secretion. Under the influence of substances, including thrombin, collagen, epinephrine, vasopressin, platelet-activating factor, and arachidonic acid metabolites, released from sites of tissue injury, platelets are activated and undergo robust rheologic transformation (Fig 1). When components of the subendothelial matrix then become exposed to circulating blood, platelet glycoproteins

Table 1—*Platelet Receptors, Surface Molecules, and Intracellular Constituents Contributing to the Inflammatory Response During Critical Illness*

Platelet Components	Stimuli	Effects
Receptors and surface molecules		
Integrins		
GP IIb/IIIa	Fibrinogen, fibrin	Platelet aggregation
G-protein-coupled receptors		
Protease-activated receptors	Thrombin	Platelet activation
Thromboxane receptors	Thromboxane A_2	Activation, aggregation
ADP receptors	ADP	Activation, aggregation, altered rheology
P-selectin	Inflammation and tissue injury	Adhesion, cellular communication
Intracellular constituents		
Cytoplasmic substances		
Serotonin	Inflammation and tissue injury	Platelet activation
Epinephrine	Inflammation and tissue injury	Platelet activation
α Granules	Inflammation and tissue injury	Secretion facilitates coagulation
Dense granules	Inflammation and tissue injury	Release ADP, calcium, serotonin

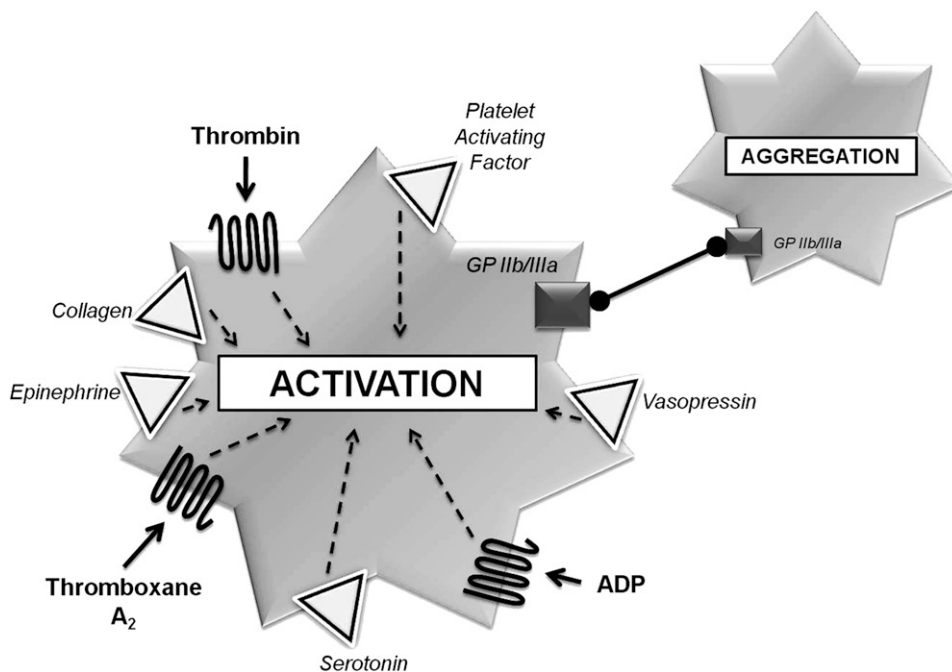ADP = adenosine diphosphate; GP IIb/IIIa = glycoprotein IIb/IIIa.

FIGURE 1. Key participants in human platelet activation and aggregation. ADP = adenosine diphosphate; GP IIb/IIIa = glycoprotein IIb/IIIa.

and von Willebrand factor (vWF) mediate an intense adhesive process. Platelet aggregation firmly ensues, largely supported by the GP IIb/IIIa receptor, and these events are then ultimately reinforced by a potent milieu of vasoactive compounds secreted from the galvanized platelet offensive.[8]

Platelets in Host Immunity

Platelets have long been considered by many to be vital participants in immune processes and, hence, potentially key instigators in a number of common inflammatory diseases. Once activated, platelets release numerous secretory products and have been shown to express a multitude of receptors involved in the inflammatory response (Table 1). In atherosclerosis, for instance, activated platelets can release adhesive ligands such as P-selectin. P-selectin is capable of creating a phospholipid-rich platform that then facilitates the recruitment of mononuclear cells and lymphocytes to the atherosclerotic plaque.[7] Platelet activation has been associated with enhanced cytokine expression in other inflammatory conditions, including acute coronary syndromes, coronary stent restenosis, and solid organ transplant rejection.[12,13]

Platelets also interact directly with other inflammatory cells, helping to engineer both physiologic and pathologic immune events. Leukocytes, for instance, are known to play an important role in host defense when recruited to sites of inflammation.[14] Although critical in helping to defend the host from invading

microorganisms, untoward sequelae of leukocyte recruitment can include tissue injury, hypoxia, and organ dysfunction.[15] Platelets have been shown to facilitate the leukocyte response, largely under the influence of P-selectin, which promotes leukocyte-platelet binding.[15,16]

Although platelets interact with most leukocyte subpopulations, it is their intimate relationship with neutrophils that seems to drive their primary role in host immunity. Endothelial-bound platelets can induce "secondary capture" of neutrophils by first facilitating platelet-neutrophil interactions and then by directing subsequent neutrophil-endothelial cell contact. Neutrophils also are capable of rolling along a template of adherent platelets—an event regulated by numerous adhesive receptors and promoted by shear forces and alterations in cellular structure.[17] This rolling phenomenon is thought to be mediated largely by P-selectin, which directs leukocyte adherence and then supports leukocyte transmigration directly to the site of injury.[18]

Thrombocytopenia in Critical Illness

From a more clinical perspective, alterations in platelet number and function are frequently recognized in association with critical illness. In particular, the development of thrombocytopenia is commonplace, with an incidence ranging from 20% to nearly 50% across a spectrum of intensive care settings.[19,20] When present, thrombocytopenia is independently associated with increased morbidity and mortality.[19,20]

What has been less well established is a causal relationship between thrombocytopenia and critical care outcomes. Whether thrombocytopenia represents platelet activation and consumption as a primary pathologic event or merely serves as a marker for disease severity is unknown. This uncertainty is a consequence of the myriad of conditions known to influence circulating platelet numbers in heterogeneous ICU patients, rendering it difficult for investigators to account for all potential confounders in clinical research. Critically ill individuals may have diminished platelet production due to medication effects, bone marrow suppression, nutritional deficiencies, and infection. They also may have enhanced platelet elimination due to splenic sequestration, consumption related to disseminated intravascular coagulopathy, and thrombocytopenia as a result of hemodilution. Immunologically mediated thrombocytopenia and spurious thrombocytopenia also can introduce complexity into a patient's evaluation and ICU course.

Thrombocytopenia is a poor prognostic marker and a rather powerful predictor of mortality in patients with sepsis and septic shock,[21] and the magnitude of platelet reduction seems to correlate with the severity of illness.[20,22] In ALI and ARDS, the development of clinical thrombocytopenia and its influence on outcomes are poorly understood. In small patient series representing noncontemporary treatment eras, thrombocytopenia was believed to occur in as many as 50% of patients with ARDS.[18,23] The degree of thrombocytopenia has been shown to parallel the course of progressive hypoxemic respiratory failure[24] but has been inconsistently associated with mortality.[24,25] More recently, thrombocytopenia has been described as a prominent feature among patients with severe acute respiratory syndrome, a rapidly progressive coronavirus-associated respiratory illness resulting in a global outbreak of ALI and shock.[26]

Platelets in Sepsis

Activation and Aggregability

There are conflicting data about platelet function and response to stimuli in critically ill patients with sepsis. Some would suggest that the septic milieu, in part influenced by lipopolysaccharide and endotoxemia, promotes enhanced platelet aggregation, leading to microvascular obstruction and tissue injury.[27] Others have argued that aggregation and platelet responsiveness actually decrease in patients with sepsis,[28] whereas still others have suggested that activation may in fact be enhanced during sepsis but that significant platelet degranulation only occurs in those who are most severely decompensated.[29]

Gawaz and colleagues[29] found that plasma from patients with sepsis increased both the adhesion and the aggregability of normal platelets to cultured endothelium. Mavrommatis et al[22] later showed that platelet activation was significantly increased in patients with sepsis compared with healthy control subjects. Others have demonstrated that sepsis results in increased P-selectin expression.[30] On the other hand, platelet function by aggregometry and flow cytometry was shown to be decreased in studies by Yaguchi et al,[31] and Boldt et al[32] demonstrated that aggregation decreased over time in a cohort of trauma patients who later developed sepsis.

Recently, both human and murine platelets have been shown to express toll-like receptors 4 that facilitate platelet migration and deposition into tissue during sepsis.[33] It is possible that these pattern recognition receptors may represent a unique mechanism by which organ dysfunction develops in severe infection; further research, however, will be necessary to clarify this association.

Acquired deficiencies in the plasma protease ADAMTS13 also may support the enhanced platelet activation that has been described in both sepsis and the systemic inflammatory response syndrome. Nguyen and colleagues[34] reported functional decreases in ADAMTS13—the principle physiologic modulator of vWF in human plasma—among patients with sepsis. Others have demonstrated a stepwise decline in ADAMTS13 activity, which paralleled the extent of inflammatory response in small samples of critically ill ICU patients.[35]

The burden of evidence seems to support the notion that platelet activation and aggregation increase during sepsis. The result of this accelerated platelet response, and the mechanism of resulting tissue injury, is less well defined. Although small studies have shown that platelets can cause microvascular obstruction and tissue hypoperfusion, impairment in cardiac contractility,[36] and endothelial dysfunction as a consequence of platelet-induced apoptosis,[37] it is likely that a number of other poorly defined pathologic events contribute to the untoward influence of platelets on septic outcomes.

Platelet-Leukocyte Interactions

One such mechanism of injury during sepsis may center around the aforementioned role that platelets play in leukocyte recruitment. Although this likely represents an adaptive response to facilitate host defense, there is mounting evidence to suggest that maladaptive platelet-leukocyte interactions can result in tissue injury.[38] In a study of polymicrobial sepsis, Asaduzzaman et al[39] found that significant lung injury resulted from enhanced pulmonary

infiltration of platelet-bound neutrophils. Other investigators have demonstrated that inhibition of platelet-associated neutrophil recruitment can mitigate all forms of end-organ damage, helping to establish a causal relationship between platelet-neutrophil interactions and the pathologic injury seen in severe sepsis.[40,41]

It has been proposed that platelets recruit neutrophils to sites of tissue injury and inflammation, resulting in subsequent damage through a variety of mechanisms. Platelet-neutrophil aggregates may become trapped within narrow sites of organ microvasculature, leading to regional ischemia. Kirschenbaum and colleagues,[42] for instance, showed that formation of these aggregates had a pronounced effect on altering blood rheology in patients with sepsis, a process that the investigators believed contributed significantly to impairments in perfusion. Platelets also may adhere directly to inflamed endothelial cells and promote secondary capture of toxic circulating leukocytes. This mechanism has been supported by several small studies in which targeted inhibition of platelet-specific ligands on neutrophils reliably attenuated sepsis-associated endothelial injury.[29,43] Circulating platelet-neutrophil complexes and platelet-stimulated neutrophil extracellular trap formation also can be seen in the patient with sepsis. These neutrophil extracellular traps are believed to represent a subset of activated neutrophils with enhanced ability to adhere, phagocytose, and produce injurious superoxide.[43] Finally, other data suggest that lymphotoxicity and lymphoid cell apoptosis may result from sepsis-induced alterations in platelet mRNA profiles.[44]

Platelets in ALI and ARDS

Dysregulated hemostasis and enhanced inflammation are hallmark pathophysiologic events associated with both ALI and ARDS. Postmortem series of patients with ARDS have shown that platelet deposition within the damaged pulmonary microvasculature is commonplace.[45] Ultrastructural examinations of lungs from patients with ARDS have consistently shown platelet accumulation and platelet-fibrin deposition occurring within pulmonary arteries, arterioles, and capillaries as well as within both the pulmonary interstitial and the alveolar compartments of affected individuals.[46]

Platelet-Specific Mechanisms of Injury

As in sepsis, platelet-neutrophil interactions seem to play a dominant role in tissue injury seen during ARDS. In a murine model of acid-induced lung injury, Zarbock and colleagues[41] demonstrated that increased neutrophil adhesion and activation resulted from thromboxane A_2 produced by platelet-neutrophil aggregates. Efforts to deplete platelets or disrupt these aggregates resulted in reduced neutrophil migration and permeability, improved gas exchange, and better survival.

Enhanced platelet activation and secretion also have been supported by several other clinical and preclinical studies of ALI. In a ventilator stress-induced model of ARDS, Yiming et al[47] demonstrated increased expression of vWF, glycoprotein Ib, and P-selectin on the endothelial surfaces of rat and mice lungs. In a bronchoscopic study of patients with lung injury, Idell and colleagues[48] found that levels of platelet-specific α-granule proteins were elevated in BAL fluid from injured tissue and directly correlated with the degree of pulmonary injury. In a study of critically ill patients, investigators not only found that in vivo platelet activation was more robust among those with acute respiratory failure but also showed that marked platelet dysfunction, characterized by impaired aggregation and prolonged bleeding time, was a typical feature in these individuals.[49]

A careful review of several currently used evidence-based therapies for ALI and ARDS provides additional insight into the potential pathologic role of platelet-mediated events. A host of clinical studies have helped to define contemporary treatment strategies for this critical illness, and several of these therapies share, in part, an ability to modify mechanisms of platelet activation and aggregation. Perhaps the most well-validated strategy to reduce mortality is the use of low-tidal-volume ventilation,[2] and, in fact, the use of injurious high-tidal-volume ventilation has been shown to upregulate both vWF and P-selectin expression.[47] Using lung-protective positive pressure ventilation, however, is associated with decreased ADP- and collagen-mediated platelet aggregation.[50] Nitric oxide, another therapy often used in ARDS/ALI despite limited data to support its routine use, has been shown to decrease platelet aggregation by reducing fibrinogen binding to the GP IIb/IIIa receptor.[51] As well, the controversial use of corticosteroids in ARDS[52] has been associated with decreased platelet activation and activity in some experimental models.[53,54] Although not suggesting that these therapies improved lung injury through their platelet-modifying effects alone, these data do support a biologic plausibility that should be considered when studying the impact of dysregulated platelet activity on patient outcomes (Fig 2).

Studies of Antiplatelet Strategies in Critical Illness

Although there is growing evidence to suggest a pathologic role for platelets in a number of inflammatory
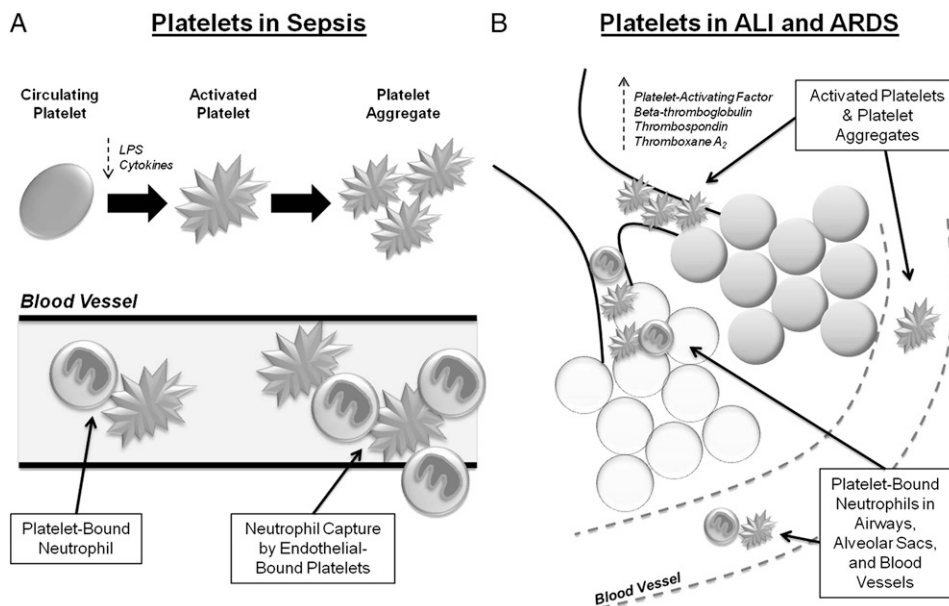
FIGURE 2. A, Influence of platelet and platelet-neutrophil interactions on the pathophysiology of sepsis and, B, ALI. In sepsis, platelets may be stimulated by tissue injury, hypoxia, cytokines, LPS, and endotoxemia, leading to microvascular obstruction, cellular necrosis/apoptosis, and an enhanced leukocyte response. In ALI, platelets and platelet-neutrophil complexes can similarly be found within the pulmonary vasculature, airways, interstitial, and alveolar compartments. ALI = acute lung injury; LPS = lipopolysaccharide.

conditions, including sepsis and ALI, there are far fewer data to support targeted antiplatelet strategies as therapeutic options for managing afflicted patients. Such a strategy, however, is not without historical merit. For years now, the cardiovascular community has been espousing the benefits of antiplatelet agents for reducing inflammation in both acute and chronic atherosclerotic diseases. With this as a platform for novel investigation, there is now burgeoning interest in platelets as therapeutic targets for patients with critical illness.

Antiplatelet Agents and Inflammation

Aspirin: Within a subset of patients enrolled in the Physicians' Health Study, a randomized trial of aspirin vs β-carotene for the primary prevention of cardiovascular disease, the use of aspirin was associated with a significant reduction in the risk of myocardial infarction predominantly among patients with the highest C-reactive protein (CRP) values.[55] This finding was among the first pieces of clinical evidence to suggest a possible antiinflammatory role for commonly used antiplatelet therapies. Aspirin also has been shown to have inhibitory effects on the activity of nuclear factor κβ, a transcription factor that is required for the expression of genes encoding a variety of inflammatory molecules.[56] In a mouse model of atherosclerosis, the normally enhanced nuclear factor κβ activity was substan-

tially reduced in animals who were treated with aspirin.[57]

Among healthy volunteers, however, there is little compelling evidence to support an antiinflammatory effect of aspirin,[58] and studies among patients with both acute and chronic inflammatory conditions have yielded mixed results. In patients with chronic, stable angina, for instance, aspirin significantly lowered CRP and inflammatory cytokine levels.[59] Conversely, in other patients with chronic ischemic heart disease, recent myocardial infarction, and acute coronary syndromes, aspirin failed to reliably reduce CRP.[60,61] In peripheral arterial disease as well, markers of platelet-mediated inflammation were not significantly decreased with aspirin therapy.[62] There is also conflicting evidence regarding the potential of aspirin to mitigate pathologic inflammatory interactions between platelets and leukocytes.[62,63]

Clopidogrel: Clopidogrel (Plavix), an irreversible antagonist of the G-protein-coupled platelet ADP receptor (P2Y12), has been shown to have a greater influence on cardiovascular risk reduction among patients at heightened inflammatory states. In a post hoc analysis of the Clopidogrel for the Reduction of Events during Observation trial, a study of prolonged clopidogrel therapy following percutaneous coronary intervention (PCI), there was a significant (44%) relative risk reduction in the combined end point of death, myocardial infarction, or stroke at

12 months for those patients in the highest tertile of high-sensitivity CRP levels.[64] Likewise, shorter-term cardiovascular events were reduced following PCI in those patients pretreated with clopidogrel who had elevated baseline CRP values.[65]

Unlike aspirin therapy, however, clopidogrel administration has been shown to reduce the secretion of adhesive ligands and to block the formation of platelet-leukocyte conjugates, with resulting decreases in leukocyte activity. In patients treated with PCI, clopidogrel reduced ADP- and thrombin receptor-activating peptide-induced expression of the platelet P-selectin.[66] Evangelista and colleagues[67] showed that clopidogrel use had a potent inhibitory effect on platelet-dependent production of reactive oxygen species in neutrophils, as well as monocyte expression of tissue factor. Klinkhardt et al[68] found that more-prolonged clopidogrel pretreatment could significantly reduce the volume of both platelet-monocyte and platelet-neutrophil aggregates following ADP stimulation, effects that correlated directly with substantial reductions in P-selectin expression. Similarly, clopidogrel therapy has been shown to reduce platelet-neutrophil and platelet-monocyte conjugates in patients across a spectrum of vascular diseases.[62,69]

Other Antiplatelet Agents: Conflicting data have come from studies of the GP IIb/IIIa receptor antagonists in inflammatory conditions. Modest levels of receptor blockade actually have been associated with increases in platelet-mediated proinflammatory effects, along with enhanced expression of P-selectin,[70] and increased release of soluble CD40 ligand.[71] Furthermore, although the synthetic small-molecule GP IIb/IIIa inhibitor eptifibatide (Integrilin) significantly reduced levels of CRP at 24 h compared with placebo in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial, levels subsequently increased beyond baseline 30 h following infusion.[72] On the other hand, abciximab (ReoPro), a chimeric Fab fragment of a monoclonal antibody with high affinity for the GP IIb/IIIa receptor, was found to suppress the usual rise in levels of circulating inflammatory markers following percutaneous transluminal coronary angioplasty.[73] Finally, among small populations of patients treated with tirofiban (Aggrastat), data have been largely inconclusive.[74,75]

Antiplatelet Agents in Critical Illness

In general, there has been limited study of antiplatelet therapeutic strategies in critical care populations. Lösche and colleagues[76] found that antiplatelet drugs were associated with a slight reduction in mortality among patients with nonsurgical critical illness and a slightly increased mortality rate among those requiring surgery. When adjusted for differences in baseline characteristics and disease severity, however, antiplatelet therapy use was associated with substantially reduced mortality in both groups.

In a single-center study of hospitalized patients with community-acquired pneumonia, 20% of whom had received antiplatelet agents for the secondary prevention of cardiovascular disease, Winning et al[77] found antiplatelet drug use to be associated with a reduction in length of stay and the need for ICU care. Later, in a retrospective study conducted in a mixed medical-surgical ICU, these same investigators found that preexistent treatment with antiplatelet agents reduced the odds ratio for mortality by nearly fivefold.[78] Even in patients with signs of active bleeding, including life-threatening intracranial hemorrhage and transfusion-dependent anemia, there still was a strong association between antiplatelet drugs and improved outcomes. This association was most robust among those patients with the greatest disease severity.[78] Although limited by the retrospective nature of these analyses and modest design challenges, these data still speak to the potential role of platelets as therapeutic targets among heterogeneous critical care populations.

Antiplatelet Agents in Infection and Sepsis

The impact of antiplatelet agents on circulating platelets and markers of inflammation during systemic infection has yet to be clarified, despite increasing study in both animal and human models. In early studies of antiplatelet drugs in endotoxemic pigs, pretreatment was found to have minimal effects on the pathogenesis of *Escherichia coli*-induced shock. Despite platelet targeting, clinical sepsis ensued in these animals, with concomitant decreases in levels of platelets along with activation of both the coagulation and fibrinolytic systems.[79] Clopidogrel also had no demonstrable effect on hemostatic or inflammatory responses of pigs infused with *E coli* endotoxin.[80] However, when specifically using clopidogrel in other animal models of sepsis, several investigators have reported that not only is platelet activation reduced but also clinical thrombocytopenia is attenuated, clot formation is decreased, cytokine upregulation is mitigated, and neutrophil recruitment may be minimized.[68,81]

Antiplatelet Agents in ALI and ARDS

Even fewer data exist regarding antiplatelet strategies in critically ill patients with lung injury. Targeted platelet depletion or disruption of platelet-neutrophil interactions in murine models of ARDS resulted in reduced neutrophil migration and permeability, improved alveolar gas exchange, and increased survival.[41] Aspirin use in an experimental

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transfusion-related ALI model did not prevent neutrophil sequestration; however, the neutrophils that infiltrated the pulmonary parenchyma were rendered incapable of causing lung toxicity.[82] Further study clearly is needed to build on these preliminary data in order to clarify the intriguing potential of therapeutic platelet targeting in lung injury populations.

Conclusions and Future Directions

The role of platelets in the pathophysiology of critical illness continues to be elucidated, particularly with respect to lung injury where our understanding is woefully incomplete. No longer are these anucleate cells considered merely executors of the thrombotic process but, instead, are clearly key contributors to the host immune response. Although initially adaptive, unregulated platelet activation during sepsis, ALI, and ARDS leads to organ hypoperfusion, pathologic tissue injury, and poor patient outcomes. Whether modulation of this platelet response will improve the high morbidity and mortality associated with these diseases remains to be seen. Small, nonrandomized clinical studies of antiplatelet strategies have yielded mixed results but should prompt additional investigation.

Following on the heels of these early discoveries, future study may further capitalize on the relationship between platelets and platelet receptors in human critical illness. Building on circumstantial evidence from trials of contemporary antiplatelet therapies, some investigators have begun to focus greater attention on the role of adenosine and its myriad of receptors on the pathobiology of inflammation. During conditions of high metabolic stress, as seen in acute tissue injury and sepsis for instance, extracellular adenosine concentrations often are markedly increased.[83] Adenosine is believed to play an important role in preventing neutrophil infiltration into vulnerable tissue,[84] and a growing body of data suggests a possible role for adenosine in modulating adaptive immune response to critical illness.

Likewise, increased attention has and should be directed toward the influence of platelet polyphosphates as both proinflammatory and procoagulant mediators during acute illness. Recent investigation has shown that polyphosphates help to trigger fibrin formation and facilitate capillary leakage, which is commonplace among ICU patients. The polyphosphates also seem to play a role in preserving cellular integrity and modulating neutrophil response during inflammation.[85]

With advances in high-throughput experimental technologies, researchers are now beginning to characterize the full complement of transcripts and functionally relevant proteins that contribute to the versatility and complexity of platelets in human disease.[86] A more-integrated understanding of platelet biology undoubtedly will allow for improved clarification of the adaptive and maladaptive influences of platelets in critical illness. The potential for identifying molecular signatures of pathologic platelet activity also could provide an ambitious platform for studying patient variation in disease response, establishing novel risk stratification tools, and developing future therapeutic targets.

As critical care investigators and practitioners, we only recently have begun to understand the true versatility of the human platelet. A more concerted, multidisciplinary effort to unravel the mysteries of the platelet during critical illness clearly will be important if we hope to minimize the devastating impact of sepsis, ALI, and ARDS on an ever-expanding patient population.

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