Linking Genetics to ARDS Pathogenesis

The Role of the Platelet

John P. Reilly, MD, MSCE

Jason D. Christie, MD, MSCE

Philadelphia, PA

ARDS is a complex syndrome, characterized by damage to the alveolar-capillary barrier resulting in increased permeability in the setting of an amplified inflammatory response. The role of the activation of clotting pathways in this process has been increasingly recognized, including the significant impact of platelets on ARDS pathogenesis.¹⁻³ In a steady state, inactive platelets circulate in blood and promote endothelial barrier integrity.⁴ However, in the setting of critical illnesses (eg, sepsis), several overlapping mechanisms activate platelets, resulting in platelet aggregation, platelet-leukocyte complex formation, and release of the granule contents of the platelet cell, including molecules that enhance inflammation and cell adhesion. While platelet-mediated thrombosis in the lungs has been implicated in ARDS pathogenesis, the activation of circulating platelets results in a host of other inflammatory effects contributing to ARDS development, including augmented neutrophil migration and increased endothelial barrier permeability.³

Given the accumulating evidence for the role of platelets in ARDS, significant interest has recently developed in therapeutically targeting platelet activation and func-

tion. In mouse models of ARDS, inhibiting P-selectin-mediated platelet-neutrophil interactions protect from lung injury.² In humans, preexisting antiplatelet drugs, such as aspirin or clopidogrel, are associated with decreased risk of ARDS as well as decreased mortality among the critically ill.^{5,6} Several ongoing studies are investigating the role of antiplatelet therapy in ARDS, including the Lung Injury Prevention Study with Aspirin (LIPS-A),⁷ a multicentered randomized controlled clinical trial evaluating aspirin for the prevention of ARDS in patients at risk. While current antiplatelet agents have the potential to have therapeutic benefit in the critically ill, further enhancing our understanding of the mechanisms by which platelets contribute to ARDS may identify novel therapeutic targets or select patient subgroups most likely to respond to antiplatelet therapy.

In this issue of *CHEST* (see page 607), Wei and colleagues⁸ use an innovative approach to identify a novel genetic variant linked to platelets, which is associated with ARDS risk. Several investigators have identified genetic variants in genes implicated in alveolar-capillary barrier integrity,⁹ inflammation,¹⁰ and coagulation as risk factors for ARDS¹¹; however, variants resulting in platelet heterogeneity have not previously been linked to ARDS. Working with the knowledge that thrombocytopenia during critical illness is associated with poor outcomes,¹² and that genome-wide association studies have identified several genetic variants linked to platelet count in the noncritically ill,¹³ Wei and colleagues⁸ set out to answer several questions. First, they determined the association of single nucleotide polymorphisms (SNPs) in candidate genes with platelet count in a cohort of critically ill patients at risk for ARDS. They selected candidate genes based on previous associations with platelet count in relatively healthy populations and identified an intronic SNP in *LRRC16A* as also associated with platelet count among the critically ill. Next, the same SNP in *LRRC16A* was determined to be associated with altered risk of ARDS. Lastly, they used sophisticated statistical methods to determine whether platelet count was a causal mediator linking the *LRRC16A* genotype to ARDS risk. Decreased platelet count, measured at ICU admission, was associated with increased ARDS risk in their cohort and functioned as a partial mediator of the association between *LRRC16A* genotype and ARDS. While not proving causation, this approach

AFFILIATIONS: From the Division of Pulmonary, Allergy and Critical Care Medicine, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following conflicts: Dr Christie has received funding from the National Institutes of Health to study glycobiology and ARDS. Dr Reilly has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

CORRESPONDENCE TO: Jason D. Christie, MD, MSCE, Division of Pulmonary, Allergy and Critical Care Medicine, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, 717 Blockley Hall, 423 Guardian Dr, Philadelphia, PA 19104; e-mail: jchristi@upenn.edu

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-2701

not only identified a novel genetic risk factor for ARDS, but also provided evidence for a potential mechanism resulting in the altered risk.

The most significant limitation to the study conducted by Wei and colleagues⁸ is that the only causal mediator evaluated was a single measure of platelet count at ICU admission. Based on these data, it is difficult to determine whether the effects of platelet count on ARDS risk are a result of decreased platelet production or increased platelet activation, lung sequestration, and consumption. Additionally, platelet function may be equally as important in mediating ARDS risk as platelet count and may explain why count was only a partial causal mediator of the *LRRC16A* and ARDS association. In addition to validating their findings in an independent population, future research should evaluate the effects of *LRRC16A* on measures of platelet consumption and production, such as serial platelet counts or immature platelet fractions, as well as measures of platelet function, aggregation, and neutrophil adhesion.

Despite these limitations, Wei and colleagues⁸ have successfully identified a variant in *LRRC16A* associated with altered ARDS risk, at least partially mediated via effects on platelet count. *LRRC16A* encodes the protein, capping protein ARP2/3 and myosin-I linker (CARMIL), important in actin-based cellular processes.¹⁴ This protein has not previously been implicated in ARDS, and the mechanisms underlying its effects on platelet count are not completely understood. Furthering our understanding of the role of *LRRC16A* and CARMIL protein in platelet development and/or function as well as ARDS pathogenesis may identify novel therapeutic targets within platelet cellular processes with relevance to ARDS. Likewise, *LRRC16A* variation may represent a key focus for pharmacogenetic interaction in ongoing trials of aspirin therapy. Therefore, the study by Wei and colleagues⁸ provides key data to focus our near-term research efforts on the role of platelets in ARDS.

References

- Ware LB, Matthay MA, Parsons PE, Thompson BT, Januzzi JL, Eisner MD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. *Crit Care Med*. 2007;35(8):1821-1828.
- Zarbock A, Singbartl K, Ley K. Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation. *J Clin Invest*. 2006;116(12):3211-3219.
- Katz JN, Kolappa KP, Becker RC. Beyond thrombosis: the versatile platelet in critical illness. *Chest*. 2011;139(3):658-668.
- Weyrich AS, Zimmerman GA. Platelets in lung biology. *Annu Rev Physiol*. 2013;75:569-591.
- Eisen DP, Reid D, McBryde ES. Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis. *Crit Care Med*. 2012;40(6):1761-1767.
- Kor DJ, Erlich J, Gong MN, et al; US Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators. Association of prehospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients. *Crit Care Med*. 2011;39(11):2393-2400.
- Kor DJ, Talmor DS, Banner-Goodspeed VM, et al; US Critical Illness and Injury Trials Group: Lung Injury Prevention with Aspirin Study Group (USCIITG: LIPS-A). Lung Injury Prevention with Aspirin (LIPS-A): a protocol for a multicentre randomised clinical trial in medical patients at high risk of acute lung injury. *BMJ Open*. 2012;2(5):e001606.
- Wei Y, Wang Z, Su L, et al. Platelet count mediates the contribution of a genetic variant in *LRRC16A* to ARDS syndrome risk. *Chest*. 2015;147(3):607-617.
- Meyer NJ, Li M, Feng R, et al. ANGPT2 genetic variant is associated with trauma-associated acute lung injury and altered plasma angiopoietin-2 isoform ratio. *Am J Respir Crit Care Med*. 2011;183(10):1344-1353.
- Meyer NJ, Feng R, Li M, et al. IL1RN coding variant is associated with lower risk of acute respiratory distress syndrome and increased plasma IL-1 receptor antagonist. *Am J Respir Crit Care Med*. 2013;187(9):950-959.
- Madách K, Aladzsity I, Szilágyi A, et al. 4G/5G polymorphism of PAI-1 gene is associated with multiple organ dysfunction and septic shock in pneumonia induced severe sepsis: prospective, observational, genetic study. *Crit Care*. 2010;14(2):R79.
- Vanderschueren S, De Weerd A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. *Crit Care Med*. 2000;28(6):1871-1876.
- Qayyum R, Snively BM, Ziv E, et al. A meta-analysis and genome-wide association study of platelet count and mean platelet volume in African Americans. *PLoS Genet*. 2012;8(3):e1002491.
- Yang C, Pring M, Wear MA, et al. Mammalian CARMIL inhibits actin filament capping by capping protein. *Dev Cell*. 2005;9(2):209-221.

COPD in Heart Failure Are There Long-term Implications Following Acute Heart Failure Hospitalization?

Lauren B. Cooper, MD
Robert J. Mentz, MD
Durham, NC

Heart failure (HF) and COPD are major and increasing public health problems worldwide. In the United States, HF affects > 5 million adults and results in > 1 million hospitalizations annually.¹ Despite advances in the treatment of chronic HF, outcomes following acute HF hospitalization remain poor.¹ Given the neutral results of most recent HF trials, there is a need for a critical reappraisal of strategies to improve outcomes.² COPD affects > 15 million Americans, commonly occurs in patients with HF, and is associated with significant morbidity and mortality.³⁻⁵ Recognition of the impact of