Predicting the Development of Acute Respiratory Distress Syndrome
Searching for the “Troponin of ARDS”

Acute respiratory distress syndrome (ARDS) is the syndrome that defines critical care, much as coronary artery disease defines cardiology. Just as in coronary artery disease (1), a multifaceted approach, incorporating preventive strategies, early disease detection, and treatment may offer the best hope of reducing the burden of ARDS. We have had encouraging success in the area of prevention of ARDS in “at-risk” patients. Li and colleagues from the Mayo Clinic recently demonstrated that implementation of current approaches to preventing the development of ARDS, including optimal mechanical ventilation, aggressive resuscitation, reduction of transfusion, and prevention of common complications, reduced the incidence of ARDS in Olmsted County from 81 to 38.3 cases per 100,000 person-years (2). This decrease was driven by a decrease in hospital-acquired ARDS, suggesting that the preventative measures were effective.

Continuing the analogy to cardiology, early identification and treatment of patients with or at risk for coronary ischemia has been greatly facilitated by the availability of a number of biomarkers, particularly troponin. Many potential biomarkers of ARDS, including surfactant proteins, cytokines, and markers of pulmonary epithelial and endothelial injury, have been investigated, with some success. For example, combining a panel of biomarkers (IL-8, soluble tumor necrosis factor receptor-1, and surfactant protein-D) with APACHE II scores enhanced mortality prediction in patients with acute lung injury (ALI) (3). However, the identification of a clinically useful “troponin of ARDS” has proven elusive. The fact that acute myocardial infarction is a “disease” with a well-defined etiology and pathophysiology has greatly facilitated the identification of powerful diagnostic markers such as troponin. In addition, effective therapies exist for coronary artery disease, and their efficacy can be maximized by early diagnosis. ARDS, by contrast, is a syndrome—not a disease—and is diagnosed based on fulfillment of a set of “criteria” that themselves have a high sensitivity but low specificity for the pathologic condition of ARDS. In addition, ARDS has a complex multifactorial etiology, and an incompletely understood pathophysiology. Worse yet, there are no effective interventions for ARDS that if applied would harness the benefits of early ARDS detection. These issues all pose substantial challenges to the identification of a useful biomarker for ARDS.

In this issue of the Journal, Agrawal and colleagues (pp. 736–742) provide evidence for the utility of biomarkers, both alone and in combination with clinical prediction indices, in determining which critically ill patients will develop ARDS (4). They studied 230 patients presenting to the emergency department who required intensive care unit admission but did not have ALI. Furthermore, patients who developed ALI within the first 6 hours were excluded from analysis, to reduce the likelihood of enrolling patients with established early disease. The plasma biomarkers angiopoietin-2 (Ang-2), von Willebrand factor, IL-8, and/or soluble receptor for advanced glycation end products (sRAGE) were chosen a priori based on their potential roles in the pathogenesis of ALI. Elevated Ang-2—but not von Willebrand factor, sRAGE, or IL-8—predicted the development of ARDS. Ang-2 performed comparably to the Lung Injury Prediction (LIP) score, a validated clinical prediction score (5). Interestingly, the addition of plasma Ang-2 measurements to the LIP score improved the prediction of ALI development. Although the LIP score has a high negative predictive value, its positive predictive value of 18% is low (5). This means that less than one in five patients with a high LIP score will develop ALI, restricting its utility as a tool for targeted early intervention. Combining raised Ang-2 with the LIP score improved the positive predictive value to 40%, suggesting that this combination may be a better prediction tool for targeting early intervention and therapy.

Plasma Ang-2 demonstrates growing promise as a biomarker for ARDS (6) and sepsis (7). Ang-2 concentrations correlated with increases in pulmonary endothelial permeability and both presence and severity of ALI/ARDS in the critically ill patients with and without sepsis (8). Ang-2 concentrations mirrored disease severity and predicted the development of shock and death in emergency department patients with suspected infection (7). Biomarkers are perhaps most useful when they tell us something about the pathophysiology of the disease. A biomarker that both closely reflects disease presence and/or severity and mediates the responsible biologic processes links molecular mechanisms to diagnosis. Such a biomarker would both aid in the prediction and/or diagnosis of ARDS and focus therapeutic strategies on the key pathogenic mechanisms contributing to ARDS. Intriguingly, Ang-2 appears
to directly worsen endothelial permeability. Mice with one functional Ang-2 allele are protected from lung injury and vascular leak (7). Serum from both patients with sepsis (7) and those with ALI (6) disrupts endothelial barrier function, via a mechanism that is blocked via Ang-2 blockade (6, 7). These deleterious effects of Ang-2 on the endothelial barrier function appear to be mediated via a conditional antagonism of the tyrosine kinase receptor Tie 2, which is important in maintaining endothelial junctional integrity.

There are some limitations to be considered. The proportion of patients within the cohort who developed ALI within the target time frame is relatively small, emphasizing the need for validation of these important findings in a larger cohort. The patient cohort is quite specific, namely critically ill patients presenting to the emergency department that do not have ALI at intensive care unit admission. Additional studies will be required to determine whether these findings are generalizable to other critically ill patient populations. Unfortunately, the lack of a bedside assay for Ang-2 means that it is difficult to operationalize this knowledge at this time. Finally, despite the authors making considerable effort to collect blood samples early in the course of critical illness in these patients, many samples were drawn after the actual development of ALI.

In conclusion, the current study yields important insights regarding the utility of Ang-2 as a biomarker to predict ARDS. Ang-2 appears to be particularly useful when used in combination with the LIP score. Given the potential for a pathogenic role of Ang-2, these findings suggest that alterations in endothelial permeability may be a key early event in ARDS. More broadly, the development of strategies to prevent ARDS is becoming a key research priority in our efforts to reduce the disease burden of ARDS (9). One example of a prevention trial is the LIPS-A trial evaluating the efficacy of aspirin to prevent ALI (10). A key step in enhancing the feasibility of these studies is the accurate identification of patients at high risk for developing ARDS. Agrawal and colleagues deserve congratulations for their important new insights into the early identification of ALI in the critically ill.

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References


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Statins and Sepsis
Potential Benefit but More Unanswered Questions

Statins modulate pathogenic mechanisms important in the development of severe sepsis (1). In this issue of the Journal, the ANZ-STATInS Investigators (pp. 743–750) report the findings of a high-quality phase-2 randomized, placebo-controlled, multicenter trial of 250 patients with severe sepsis to determine if enteral atorvastatin 20 mg daily for up to 14 days improved biological and clinical outcomes (2). The study investigated two cohorts of patients, those who were statin naive (n = 173) and those who had received preadmission statins (n = 77). The primary outcome was plasma interleukin-6 (IL-6). There was no difference in plasma IL-6 or other secondary clinical outcome in the overall population or in the subgroup of patients who were statin naive. However in the subgroup of prior statin users, atorvastatin decreased IL-6 and reduced mortality.

This study raises several important questions.

WAS THE TREATMENT REGIMEN USED IN THIS STUDY APPROPRIATE?

Why, in this well-designed and executed study, did atorvastatin fail to show any biological or clinical evidence of effectiveness in statin-naive patients with established sepsis? A simple answer may be that statins are not effective in this population. However it is worth considering the treatment regimen used in this study.