The Renin–Angiotensin–Aldosterone System in COVID-19–related and Non–COVID-19–related Acute Respiratory Distress Syndrome

Not So Different after All?

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus enters pulmonary and myocardial cells by the binding of the spike viral protein to the ACE2 (angiotensin-converting enzyme 2) receptor, a key actuator in the renin–angiotensin–aldosterone system (RAAS). Thus, in coronavirus disease (COVID-19), RAAS has been directly implicated in the pathogenesis of acute respiratory distress syndrome (ARDS) as part of the host tissue response. ACE2 catalyzes the conversion of angiotensin II (AngII) to Ang-(1-7). When ACE2 is not present, AngII remains at increased levels, stimulating vasoconstriction, the production of inflammatory cytokines, and pulmonary fibrosis (1). Ongoing investigations of the RAAS in COVID-19 include how this pathway regulates susceptibility to SARS-CoV-2 infection, severity of illness, and how therapeutics might prevent or mitigate severe disease.

Severe COVID-19 is characterized by ARDS, a syndrome marked by noncardiogenic pulmonary edema and hypoxemia that results in death without mechanical respiratory support (2). Since the initial report in 1967, ARDS has been described to result from seemingly heterogenous insults, ranging from direct pulmonary contusions and pneumonia to indirect causes such as pancreatitis and sepsis (3). Recent advances in the field have also uncovered biological heterogeneity, which associates with different clinical outcomes (4). Despite clinical heterogeneity, lung biopsies and postmortem analyses of patients with ARDS feature diffuse alveolar damage with hyaline membrane formation and destruction of type 1 alveolar epithelial cells followed by proliferation of type 2 alveolar cells and fibrosis.

Even with a unifying cause of COVID-19, SARS-CoV-2 infection has one of the most protean presentations of any disease, and studies have found that COVID-19 ARDS phenotypes are also heterogeneous (5). Given the centrality of the RAAS to SARS-CoV-2 infection, it stands to reason that involvement of this pathway could be central to the lung injury involved in COVID-19 ARDS. A better understanding of the mechanisms driving COVID-19 ARDS compared with "classical" ARDS could lead to novel treatment options for this devastating illness.

In this issue of the *Journal*, Gerard and colleagues (pp. 1024–1034) present novel data on key RAAS enzymes in the lung and blood of patients with COVID-19 ARDS and non–COVID-19 ARDS (6). The study evaluated postmortem lungs from patients with COVID-19 ARDS compared with historical controls (both COVID-19–negative ARDS and non–lung injured samples). Using immunohistochemical staining, the major finding was that ACE and ACE2 expression in the lungs of COVID-19–negative and –positive ARDS were remarkably similar. They found increased lung ACE2 and reduced lung ACE expression in patients with COVID-19–positive and –negative ARDS compared with uninjured control subjects. ACE2 was increased selectively in pulmonary endothelial cells, whereas ACE was downregulated in both endothelial and type II epithelial cells (AT2) in the ARDS cohorts. One difference between COVID-19–positive and –negative ARDS groups was that AT2 cell numbers were reduced in COVID-19–positive compared with COVID-19–negative ARDS. This finding could represent viral induced apoptosis of AT2 cells in the COVID-19 cohort. Alternatively, because the non–COVID-19 ARDS samples were obtained from patients undergoing open lung biopsy (some of whom presumably recovered) as compared with the postmortem COVID-19 samples, the increased AT2 cells in non–COVID-19 ARDS may just represent AT2 hyperplasia, a known mechanism of lung injury repair (7). Serum concentrations revealed trends consistent with tissue expression, including increased concentrations of ACE2 and decreased concentrations of ACE, in both COVID-19– and non–COVID-19–related ARDS relative to controls. Consistent with increased ACE2 expression, the authors found increased Ang-(1-7) concentrations in COVID-19–related and non–COVID-19–related ARDS.

These findings may be counterintuitive to the presumed pathophysiology related to ACE2-induced endocytosis as a result of SARS-CoV-2 binding and relative imbalance favoring AngII activity relative to Ang-(1-7) (8). This imbalance has been suspected of being proinflammatory and vasoconstrictive, perpetuating acute lung injury in patients hospitalized with SARS-CoV-2 infection. Furthermore, although this has been thought to be unique to COVID-19–related ARDS, findings by Gerard and colleagues suggest this may be ubiquitous to ARDS regardless of etiology. However, as the authors suggest, their results may be explained by several possibilities, and similar results have been seen in other case series comparing patients who died from respiratory failure from COVID-19 with those who died from respiratory failure from influenza (9). One potential explanation for increased ACE2 in the lungs of patients with COVID-19 could be that this represents increased susceptibility to both COVID-19 infection and disease severity. Alternatively, their findings could also represent an end-stage process, associated with a relatively late compensatory upregulation of ACE2 in lung tissue and sera only seen late in the course of SARS-CoV-2 infection. Perhaps serial sampling of the alveolar space with BAL might provide insight on this issue. Without sampling over the time course of COVID-19 infection, it will be hard to disentangle whether these findings represent an adaptive or maladaptive response.

It is also important to recognize that quantification of angiotensins is associated with specific challenges. Significant metabolism and degradation of the peptides can occur *ex vivo* during

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serum incubations because of the presence of various angiotensinsases in blood. A preferred method to minimize peptide metabolism is to use an inhibitor cocktail, preventing metabolism (and clotting of blood), and solid-phase extraction (C18, C8, or phenyl matrix) of the plasma fraction to concentrate the peptides and remove interfering substances prior to assay using radioimmunoassays (10). Previous pilot studies using this technique reported circulating levels of AngII in the 20 pM range (20 pg/mL) among patients negative or positive for COVID-19 with moderate and severe respiratory failure (8). In contrast, Gerard and colleagues found AngII undetectable (<0.3 pg/mL) in the majority of their serum samples for both control and COVID-19 groups, perhaps reflecting *ex vivo* metabolism of AngII in the serum samples.

Their findings, if further validated, have several implications for both COVID-19–related and non–COVID-19–related ARDS. First, although cellular entry and destruction of ACE2 has been implicated in COVID-19–related ARDS, its contributions to non–COVID-19–related ARDS have been thought to be less relevant. However, if ACE2 plays a key role in non–COVID-19–related ARDS, therapeutic approaches in patients with COVID-19–related ARDS may have similar efficacy in non–COVID-19–related ARDS. Second, it would be important to carefully evaluate ACE2 expression in the lung compartment (early versus late after symptom onset) and how serial measurements of angiotensins and peptidases change over time as well as before and after therapy in patients hospitalized with COVID-19–related ARDS. These investigations may shed light on the interplay of clinical severity, the time course of illness, and response to treatment. Using therapies from successful COVID-19 clinical trials and applying them to non–COVID-19 ARDS would be a tremendous downstream impact from clinical trials conducted during the pandemic. These data from Gerard and colleagues are an important step in uncovering the role of the RAAS in COVID-19 and ARDS. ■

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Metabolic Risk Factors and the Development of World Trade Center Lung Disease

Longitudinal epidemiologic studies have shown that long-term exposure to particulate matter (PM) air pollution can be associated with steeper loss of lung function over time (1). Metabolic syndrome (MetSyn), which is characterized by a combination of metabolic risk factors such as dyslipidemia, hypertension, large abdominal girth, and poor glycemic control (2), has also been associated with lower lung volumes, more rapid function decline, and developing asthma (3–5). Less is known, however, about how PM exposure and metabolic risk factors longitudinally synergize in causing respiratory disease. This is an important public health question given the overwhelming prevalence of obesity and MetSyn and the wide population exposure

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