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∂ Reply to Akin *et al*.

From the Authors:

We thank Akin and colleagues for their comments on our paper (1). We agree fully that attenuated signaling through the classical axis of the renin–angiotensin system (RAS) best explains the RAS abnormalities observed in severe coronavirus disease (COVID-19). We hold this view for reasons we elaborate on in our paper's discussion. Nevertheless, whereas reduced signaling may be the simplest and most reasonable explanation of the pattern of RAS

biomarkers observed in COVID-19, it is important to acknowledge the limitations of these observations.

Akin and colleagues state that inappropriately low plasma aldosterone with elevated plasma renin implicates ACE-1 (angiotensin-converting enzyme-1) dysfunction arising from endothelial injury. This interpretation represents one possibility and is supported by the elevations in angiotensin-I/angiotensin-II ratios that are reported in patients with distributive shock (2). In COVID-19 specifically, a small pilot study found that angiotensin-II vasopressor therapy was associated with robust hemodynamic responses and improvement in multiple physiologic indices versus controls (3). However, other abnormalities may be present, for example, angiotensin-II type-1 receptor availability and signaling decrease in sepsis (4). Multiple, even redundant, impairments within a single system represent a common element in critical illness. Such broad dysfunction likely contributes to the limited historical success of novel therapeutics in critical care trials, where the test agents often only target a small subset of pathways. Therefore, we hesitate to attribute RAS abnormalities in COVID-19 acute respiratory distress syndrome (ARDS) to any singular injury or aberrant process.

The abnormalities in renin/aldosterone ratios in COVID-19 discussed by Akin and colleagues are compelling and align with observations in sepsis and vasoplegia after cardiac surgery (5, 6). Although these findings could suggest an attenuated RAS, we note they are not conclusive evidence and must consider that other mechanisms could contribute to them. For example, heparin suppresses aldosterone synthesis and is commonly administered in these patient populations.

We agree with the authors that renin/aldosterone ratio may be useful and "stronger" than renin alone as a biomarker. Potential limitations of this assay, particularly in a point-of-care setting, include weighing the degree of increased performance against the cost, feasibility, and interpretability of a single analyte versus two, particularly given that renin alone has shown strong performance in identifying hypoperfusion, predicting response to angiotensin-II therapy, and prognosing outcome in shock (7, 8).

More importantly, we stress that the key biologic implication of our study remains that in COVID-19 critical illness, disease processes are likely dynamic. As early as 1982, Nikuwa and colleagues showed in the *Journal* that canine experimental inflammatory lung injury induces ACE-1 shedding from the pulmonary endothelium (9). This shedding transiently increased both systemic and alveolar ACE-1 activity before the plasma ACE-1 activity subsequently fell to below baseline concentrations. Notably, in our cohort, we did not see renin elevations until Day 3 (1), and others have reported angiotensin-II decreases over time in COVID-19 ARDS (10). Although at Day 0, we found no correlation between renin and ACE-2 ($R_{adj} = 0.01$; $P = 0.95$), a correlation emerged by Day 3 ($R_{adj} = 0.26$; $P = 0.0045$ at Day 3) and strengthened over time ($R_{adj} = 0.47$; $P < 0.0001$ at Day 7). Therefore, both RAS states may occur, but at different times in the course of the disease, with initial pulmonary RAS excess exacerbating inflammatory injury before progressing to a systemic RAS deficiency impairing cardiorenovascular function. More studies are needed to understand the RAS in COVID-19 and ARDS, its evolution as disease progresses, and how this system can best be leveraged to clinical advantage. ∎

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Erratum: Air Pollution, Genetic Factors, and the Risk of Lung Cancer: A Prospective Study in the UK Biobank

For the convenience of our readers, the *Journal* is replacing the online version of the article with a corrected version. ∎

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