Shock, Publish Ahead of Print

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Why the use of angiotensin II may be a fatal mistake in COVID-19

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While the understanding and evidence of the novel strain of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is growing at an exponential rate, the speculation of potential therapies continues to outpace what is known. This has led many to draw clinical conclusions from inadequate data sets from publications with small sample sizes in a patient population with medical conditions that are also not currently well understood. Because SARS-CoV-2 relies heavily on the angiotensin converting enzyme (ACE) 2 pathway, many investigators have generated hypotheses that consider augmentation of this system as a potential treatment option.(1-4) We read with interest the article recently published by Busse et al suggesting a potential benefit of the use of angiotensin II and more recently by Sanders et al., omitting this recommendation, within critically ill populations afflicted with SARS-CoV-2.(5, 6)

Although the ACE2 receptor appears to play an integral role in cell entry, the downstream influence on this pathway may be responsible for a number of the complications seen within this illness. A balance of ACE and ACE2 is required among the multiple angiotensin pathways as inappropriate regulation has the potential to have catastrophic complications, some of which were noted within clinical trials of angiotensin II.(7-10) Dysregulated ratios of ACE to ACE2 concentrations have demonstrated potentially detrimental local effects on organ function, which is thought to be secondary to loss of counter regulatory effects within these localized tissues.(9,

10) These coronavirus species down regulate both the ACE2 receptor and pathway, thereby favoring diversion to the ACE pathway.(2, 3) Enhanced function of the ACE pathway has been associated with organ dysfunction, fibrosis, volume dysregulation, increased inflammation and hypercoagulation.(9, 11, 12) In contrast, researchers have shown a protective effect of the ACE2 pathway on lung injury thought to be largely due to shunting of the pathway to the production of the peptides angiotensin 1-7 and 1-9 in some alternative conditions.(12-16)(12-16)Early evidence by Liu et al. in SARS-CoV-2 patients suggests that concentrations of angiotensin II (Ang II) are markedly elevated. This observation , supports the theory that the precursors Angiotensin I and Ang II are shunted away from the ACE2 pathway a contrast to the findings of the Ang II trials where most patients had low circulating levels of Ang II.(7) Liu and colleagues went on to show a correlation with elevated Ang II concentrations and SARS-CoV-2 viral concentrations – whether this is causative or associative remains unknown.(17)(17)(17) However, the suggestion by researchers that increasing the presence of Ang II may reduce viral uptake is conflicting with this evidence.(5, 18) For example, elevated Ang II concentrations correlated with worsening lung injury and impeded gas exchange, as PaO2/FiO2 concentrations were significantly lower in those patients with higher Ang II concentrations.(17)(17) This, however, is not specific to the SARS –CoV-2 pandemic as the dysregulation of ACE2 has been associated with significant lung injury and acute respiratory distress syndrome (ARDS), leading to the development and research of recombinant ACE2 and angiotensin 1-9 for investigation in the treatment of ARDS.(10, 12, 14-16) Therefore, it becomes counterintuitive to administer further angiotensin II in a setting of already elevated concentrations, particularly in the setting of down regulation of the protective byproducts of ACE2 (angiotensin 1-9).

Previous studies have speculated that the lungs are the primary producers of Ang II due to a disproportionate activity ratio of ACE to ACE2 present.(9) This leads to the hypothesis that many of the complications seen within the COVID19 illness are that of angiotensin II toxicity, and considering the similarities of the current presentation of SARS-CoV-2 with unbridled angiotensin II activity, this hypothesis may not be far off. Predominance of Ang II via the ACE pathway rather than the protective pathway of Ang 1-7 and Ang 1-9, which is diminished by ACE2 down regulation, is associated with vascular dysfunction, fibrosis and thrombotic complications. All of these consequences are currently being observed in the SARS-CoV-2 population.(1, 8, 10, 11, 19-21) Additionally, Ang 1-7 has been shown to play an important role in cardiac protective effects and potentially improves cardiac function.(21) This allows consideration that elimination or down regulation of this pathway and disproportionate toxicity of Ang II may result in the increasing rates of cardiac dysfunction and myocardial injury that is being observed in this population.(4) Similarly, administration of Ang 1-7 in animal models has shown marked reduction of organ fibrosis. (12) It should also be noted that Ang II has significant influence on coagulation. Animal models have identified a proinflammatory and prothrombotic expression via the CD40 and very late antigen-5 resulting in significant microvasculature dysfunction.(20) These pathways have exhibited enhanced platelet aggregation and thrombin generation, as well as production of inflammatory cytokines and reactive oxygen species (ROS). Interestingly, activated protein C administration reduced concentrations of ACE and increased concentrations of ACE2; thus, reducing Ang II concentrations and increasing Ang 1-7.(22) Reduced vascular inflammation and a reduction in renal failure was also noted. The renin-angiotensin system pathway and the balance between Ang II, plasminogen activator inhibitor (PAI), bradykinin, and tissue plasminogen activator (t-PA) has been documented. Increasing

concentrations of angiotensin II result in a paralleled increase in PAI-1, and subsequent inhibition of fibrinolysis.(19) The consequence of Ang II downstream effects may be the thrombotic, particularly microthrombotic complications of SARS-CoV-2.(23) This phenomenon is even further highlighted by the landmark trials utilizing Ang II for the treatment of distributive shock that resulted in the U.S. Food and Drug Administration issuing a warning for thrombosis.(7) These coagulation consequences of Ang II could be the cornerstone of the coagulopathy being seen within this illness.

Lastly, when compared to placebo in the acute respiratory distress syndrome (ARDS) population, administration of ACE2 and subsequent decline in Ang II concentrations, have been shown to blunt the rise in IL-6, a cytokine that currently is correlated with the risk of multi-organ dysfunction and respiratory failure in the SARS-CoV-2 population.(12-16, 24) It is well known that Ang II is responsible for regulation of IL-6 leading, many to speculate that this illness and subsequent hyperinflammatory response to the SARS-CoV-2 virus may largely be driven by Ang II and an imbalance of ACE/ACE2. This imbalance and ACE/Ang II predominance has additionally shown a substantial worsening in ventilation perfusion mismatch and progression/incidence of ARDS.(1, 16) These findings may be related to the severe shunt, despite compliant lungs, being observed within the SARS-CoV-2 infected patients.

While the evidence is largely anecdotal and extremely limited at this time, there is a strong concern that much of the pathology of this illness may be explained by Ang II/ACE hyperactivity and that further perpetuation of the Ang II pathway may be placing proverbial fuel on the fire and may explain a large amount of the downstream sequelae of this illness. At the end of the day as health care professionals we have all taken an oath to first do no harm. Given the availability of alternative hemodynamic support therapies and the theorized detrimental

effects Ang II has in SARS-CoV-2 pathophysiology, the potential risk of administering Ang II in this population may outweighs any hypothetical benefit.

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Figure 1. angiotensin pathway