Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

The Renin-Angiotensin-Aldosterone System in Coronavirus Infection—Current Considerations During the Pandemic

THE renin-angiotensin-aldosterone system (RAAS) is a complex peptide cascade that has a prominent role in multiple important physiological processes such as vascular tone, vascular permeability, and myocardial remodeling.[1–3] The pharmacologic modulation of this system with agents such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBS) has resulted in major clinical benefits in the medical management of hypertension and heart failure.[3] Furthermore, the consequences of this pharmacologic blockade of the RAAS in perioperative cardiothoracic and vascular practice has been well recognized, leading to the emergence of rescue therapies for support of vascular tone.[4,5]

The severe acute respiratory syndrome coronavirus-2 infects human cells such as alveolar endothelium in the lung by binding to the membrane receptor angiotensin-converting enzyme 2 (ACE2).[1–3] Although the physiological functions of ACE2 include counteracting the effects of RAAS activation, it also functions as a membrane receptor for the coronavirus.[1–3] This binding results in endocytosis of the viral complex with consequent local activation of the RAAS, resulting in acute lung injury that may progress to adult respiratory distress syndrome.[1,2,6,7]

The purpose of this freestanding editorial is to highlight the considerations concerning the RAAS in patients presenting with severe coronavirus disease 2019 (COVID-19). This perspective will focus on the clinical relevance of these considerations to inform the management of these challenging patients.[8–11] The references provide further detail for healthcare teams as they manage the demands of the pandemic at their respective institutions.

The Prevalence of Exposure to RAAS Inhibitors in Patients With COVID-19

The prevalence of coexisting hypertension has been estimated to be in the range of 10% to 25% among patients presenting with COVID-19.[11–14] The coexisting conditions such as hypertension, older age, diabetes, and cardiovascular disease all have been reported to be more common in patients with severe COVID-19 requiring intensive care.[14–17] The comorbidities, including hypertension, also have been associated significantly with adverse outcomes in COVID-19 such as adult respiratory distress syndrome, cardiovascular compromise, and mortality.[14–18]

Since the comorbidity of hypertension has been associated with severe COVID-19 and its consequences, the question has emerged about the role of RAAS inhibitors such as ACEIs and ARBS in the pathogenesis of severe COVID-19. Given that these RAAS inhibitors are common therapies for hypertension and that they may upregulate the expression of ACE2, the clinical concern has been formulated that therapy with these agents may increase the risk and severity of coronavirus infection.[19–22] There is currently insufficient evidence to address this question in a definitive fashion.[1,14] The published literature both in preclinical and clinical studies has conflicting results about the potential for harm regarding the interactions between RAAS inhibitors and coronavirus 19. Further trials will likely focus on the current evidence gaps related to this question in severe COVID-19, including mechanisms, the prevalence of RAAS inhibitors, and careful correlation of this prevalence with clinical outcomes.[1,18,19]

Possible Benefits of RAAS Inhibitors in Patients With COVID-19

Although hypertension and consequent exposure to ACEIs and ARBS are likely common in severe COVID-19, this association does link to causality, as outlined above.[23,24] There also may be confounding by association here in that patients with severe COVID-19 are more likely to be hypertensive and older and have diabetes. This comorbidity burden rather than the associated drug therapy may better explain the adverse outcomes in coronavirus infection.[17–19]

In contrast, animal studies clearly have documented that ACE2 may have a protective role in acute lung injury related to coronavirus infection.[25,26] Functional ACE2 typically converts angiotensin II to angiotensin 1-7, thereby reducing the

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adverse effects of angiotensin II via the angiotensin type I receptor in the lung that lead to acute lung injury.[1,21] Since therapy with ACEI and/or ARBS also reduces angiotensin II levels, it follows that these agents also may protect against acute lung injury in the setting of COVID-19.[1,21,27]

The evidence for the benefits ACE2 in coronavirus infection has prompted further investigations. The exogenous administration of recombinant ACE2 not only may bind circulating coronavirus to acute viral load but also could degrade angiotensin II to downregulate activation of the RAAS and protect against acute lung injury in COVID-19.[1,22,28] This fascinating dual function of ACE2 has prompted a pilot clinical trial to evaluate recombinant ACE2 in patients with COVID-19 (full details available at www.clinicaltrials.gov with trial identifier #NCT04287686). The potential therapeutic effects of ARBS in COVID-19 also have triggered a set of clinical trials (full details available at www.clinicaltrials.gov with trial identifiers #NCT04312009 and #NCT04311177). Furthermore, there are clinical trials in progress investigating the effects of ACEI in patients with COVID-19 (full details available at www.clinicaltrials.gov with trial identifiers #NCT04322786 and #NCT04318418). These trials will likely provide much-needed evidence to guide therapy with RAAS inhibitors in patients throughout the clinical spectrum of COVID-19.

RAAS Inhibitors and Vasoplegic Shock in COVID -19

Patients with severe COVID-19 also may develop vasoplegic shock with or without concomitant sepsis.[29] In the initial wave of COVID-19 in Seattle, patients with cardiovascular compromise seldom had superinfection, suggesting that the cardiovascular instability was mostly owing to the consequences of viral infection.[6] Furthermore, in this patient cohort, echocardiography also rarely identified ventricular dysfunction, although myocarditis is a possibility in this disease.[29] This latest data from the pandemic in the United States suggest that vasoplegic shock from the effects of the coronavirus is a likely clinical presentation in severe COVID-19.[6]

A possible etiology for this low systemic vascular tone in this clinical setting may be the disordered function of the RAAS.[1,21] The first possibility is that patients on ACEIs and ARBS may be at greater risk for vasoplegia in the setting of an exaggerated systemic inflammatory response, akin to what typically is observed in perioperative cardiothoracic and vascular practice.[4,5] A second possibility is that the severe alveolar endothelial damage from adult respiratory distress syndrome may disrupt the function of angiotensin-converting enzyme 1, interfering with the hydrolysis of angiotensin I to form angiotensin II.[1–3] The resulting deficiency of angiotensin II leads to loss of systemic vascular tone.[2,3] Furthermore, the resulting excess of angiotensin I also aggravates vasoplegia through the enhanced production of nitric oxide and bradykinin.[2,3] The possibility therefore exists that vasoplegic shock in severe COVID-19 may be owing to dysregulation of the RAAS with consequent angiotensin II deficiency, suggesting that exogenous administration of this vasopressor may have a unique role in this clinical scenario.[2]

Navigating the Present Status Quo With RAAS Inhibitors and COVID-19

The status quo regarding ACEIs and ARBS in COVID-19 can be confusing to clinicians on the front lines of patient care during the pandemic, given the possibilities for both benefit and harm.[14,15] This priority for clinical guidance during the coronavirus has prompted recent statements from multiple professional societies including Canadian Cardiovascular Society, European Society of Hypertension, International Society of Hypertension, European Society of Cardiology, and American College of Cardiology.[13,14] In summary, the expert consensus from all these professional societies is that patients with COVID-19 should continue their regular home blood antihypertensive regimen, even if it includes ACEIs and ARBS.[14] In patients with COVID-19 who develop shock, the vasodilator regimen with RAAS inhibitors can be discontinued.[14]

Although not addressed specifically in these multiple professional guidelines, the role of rescue therapy for vasoplegic shock also can be considered in refractory cases, including angiotensin II.[2,4,5] Furthermore, in treatment-resistant cases of COVID-19, the mechanisms for cardiogenic shock and the supportive roles of extracorporeal membrane oxygenation should be entertained early, as these considerations often can lead to therapeutic breakthroughs.[29–31]

Conclusion

The spectrum of severe COVID-19 includes significant disruption of the RAAS, with significant implications for organ dysfunction, vascular tone, as well as therapy with ACEIs and ARBS. Although clinical trials are in progress to close the current evidence gaps, the current expert consensus has recommended that in most cases, existing therapy with ACEIs and ARBS be continued. In the setting of circulatory shock, these agents may be discontinued and early consideration of therapies for medical and mechanical rescue may be lifesaving. The management of patients through this pandemic also must consider infection control to prevent further viral transmission.

Conflict of Interest

None.

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