3. Seaman JB, Arnold RM, Scheunemann LP, et al: An integrated framework for effective and efficient communication with families in the adult intensive care unit. *Ann Am Thorac Soc* 2017; 14:1015–1020
4. Adams A, Mannix T, Harrington A: Nurses' communication with families in the intensive care unit - A literature review. *Nurs Crit Care* 2017; 22:70–80
5. Davidson JE, Aslakson RA, Long AC, et al: Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. *Crit Care Med* 2017; 45:103–128
6. Moss M, Good VS, Gozal D, et al: An official critical care societies collaborative statement: Burnout syndrome in critical care health-care professionals. A call for action. *Crit Care Med* 2016; 44:1414–1421
7. Sanderson AL, Burns JP: Clinical documentation for intensivists: The impact of diagnosis documentation. *Crit Care Med* 2020; 48:579–587
8. Gray BM, Vandergrift JL, Barnhart BJ, et al: Changes in stress and workplace shortages reported by U. S. physicians treating coronavirus disease 2019 patients. *Crit Care Med* 2021; 49:1068–1082
9. Hussain RS, Kataria TC: Adequacy of workforce - Are there enough critical care doctors in the US-post COVID? *Curr Opin Anaesthesiol* 2021; 34:149–153
10. Corby S, Whittaker K, Ash JS, et al: The future of medicial scribes documenting in the electronic health record: Results of an expert consensus conference. *BMJ Med Inform DEcis Mak* 2021; 21:204–215
11. Patient Bill of Rights. Clinical Center Home Page. Available at: https://clinicalcenter.nih.gov>patientinfo>legal>billofrights. Accessed May 15, 2022

Sex, Renin Angiotensin System Inhibitors, and COVID-19 Severity: Biologic Divergence or Healthcare Disparity?*

KEY WORDS: angiotensin II; COVID-19; renin; severe acute respiratory syndrome coronavirus 2 infection; sex

Daniel E. Leisman, MD, MSCR[1,2]
Emily E. Moin, MD, MBE[2,3]

The renin-angiotensin system (RAS) has received considerable scrutiny for its potential role in the biology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia since the beginning of the COVID-19 event. Early in the pandemic, it was discovered that like the SARS-CoV-1 virus, SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE-2) protein as a receptor to gain cell entry. This process appears further augmented by cobinding of viral-ACE-2 complexes to either angiotensin-II type-1 receptors (AT1Rs) or vasopressin-V1 receptors (1). Additionally, multiple animal models consistently reported that proinflammatory AT1R signaling played a key mediating role in the development of experimental inflammatory lung injury (2). Further heightening interest in the RAS pertaining to COVID-19, there are already U.S. Food and Drug Administration-approved therapies that modulate the RAS including inhibitors of the ACE-1 enzyme (ACE-Is) as well as AT1R antagonists (AT1R blockade [ARB]) and agonists (synthetic angiotensin-II).

Subsequent biomarker studies demonstrated a dynamic course of RAS markers in severe COVID-19 that closely correlated with organ dysfunction and illness severity (3–6). Although these observations seemingly implicated an important role for the RAS in COVID-19, randomized trials to date consistently show neither benefit nor harm from RAS-inhibiting therapies (7, 8). A caveat to interpreting these trials is that all were conducted in patients with

***See also p. 1306.**

DOI: 10.1097/CCM.0000000000005613

early, mild, or moderate disease. No randomized studies to date have evaluated RAS modulation in critically ill COVID-19 patients who meet criteria for acute respiratory distress syndrome. Still, the relation of the RAS to key early disease events, such as viral cell entry, could indicate that other factors may be at play.

In this issue of *Critical Care Medicine*, Rocheleau et al (9) offer an intriguing hypothesis informed by another observation from early in the pandemic: that men with COVID-19 tend to develop more severe disease than women.

In a prospectively enrolled multicenter observational study, the authors followed 1686 patients admitted to the hospital with COVID-19 and evaluated whether biological sex was an effect modifier for the association between chronic RAS-modulating therapy and disease severity. They found that males taking preadmission ARBs had lower risk of invasive ventilation and vasopressor use versus those not taking ARBs, an association not seen among females. This association was specific to ARBs and not seen for ACE-Is. Additionally, the authors measured plasma levels of several RAS metabolites in a subset of patients and observed that males had higher plasma ACE-1 levels than females early in the disease course. This difference between sexes subsided over time.

This observational study comparing preillness medication exposures cannot—and should not—be used to inform RAS modulating treatment strategies for critically ill COVID-19 patients. However, from the perspective of understanding the biology of COVID-19, this report raises intriguing questions for future study. Perhaps more importantly, the authors' findings also highlight underrecognized sex differences that may have impact on equitable care.

One possibility supported by the present study is that the widely hypothesized potential for RAS-modulation to influence viral susceptibility is sex-dependent. The observation that exposure to ARBs, but not ACE-Is, was associated with decreased disease severity supports this notion, given that the AT1R is shown to augment the endocytosis of complexes formed between SARS-CoV-2 and soluble ACE-2: (1) ARBs are direct receptor antagonists, whereas ACE-1 inhibitors do not directly interact with AT1R. The male-specific association reported in the present study, along with the *ACE2* gene's X-chromosomal locus and relatively higher expression in males, is also consistent with this hypothesis. Although lack of a consistent signal for disease modulation from ARB in early disease has lessened enthusiasm for RAS-inhibition, reviewing these trials for evidence of effect-modification by sex may be warranted.

Distinct from whether clinical RAS modulation impacts viral susceptibility is the question of how the RAS interacts with vascular injury and inflammation in COVID-19. Sex-related differences may again prove relevant. Notably, large meta-analyses of RAS-blocking therapy report greater antihypertensive efficacy in male versus female patients (10). Pulmonary ACE-1 shedding is a well-described sequela of acute inflammatory injury (11), including in viral infection, and the higher initial plasma ACE-1 levels seen in this study in males suggest greater pulmonary vascular inflammation. A critical limitation of the present study is the inability to disentangle whether the sex-related association between ARB exposure and COVID-19 severity reflects the drugs themselves or any of the numerous other factors represented by their use: not only underlying chronic cardiorenovascular disease severity but also patients' longitudinal engagement in healthcare and medication adherence. Although this clearly precludes inferring that chronic RAS-exposure alters COVID-19 disease course, the commonality among these myriad collinear elements is nevertheless greater chronic vascular inflammation and injury.

As to whether these data can directly influence treatment of critically ill patients with COVID-19—the answer is no. First, as discussed above, an observational study of a preillness treatment exposure cannot dictate ICU treatment decisions. Second, it is notable that no randomized trials of ARBs have been conducted in critically ill COVID-19 patients. Hemodynamic tolerability is a key concern in this population given the heavy sedation that life-saving low tidal volume ventilation often requires; the combination of RAS-inhibition, and sedative-hypnotic agents can induce profound and refractory hypotension (12).

Yet, the key implication of this study involves equitable translation of research to practice. More than 60% of study patients were male, hardly atypical of COVID-19 clinical reports. Although the relative overrepresentation of male patients in clinical trials is well-documented across multiple disciplines (13), this disparity appears heightened in COVID-19 literature. Consider that although males comprise 57% of National Institutes of Health-funded trial participants,

in the pivotal Randomized Evaluation of COVID-19 Therapy-Dexamethasone Trial (RECOVERY-DEX), which established dexamethasone as standard-of-care in COVID-19 critical illness, 73% of patients were male (14). Similar imbalances occur in major basic and translational advances in COVID-19 biology (e.g., male-only animal experiments), making them vulnerable to missing potential sex-related differences. The higher observed baseline disease severity of male patients in COVID-19 trials suggests sex differences are indeed present. However, the sex-based differences in risk associated with outpatient medication use identified by Rocheleau et al (9) may indicate clinically relevant sex-stratified effects regardless of whether they are biologically intrinsic to COVID-19. These findings may be a canary in the coal mine for mechanisms and treatments we currently accept as sex-agnostic. Whether our clinical knowledge about what works for severe COVID-19 is really just what works for men with severe COVID-19 is an uncomfortable question, but one we need to ask.

In summary, the study by Rocheleau et al (9) proposes and offers preliminary data to support a novel hypothesis on the interaction of sex and the RAS in SARS-CoV-2 infection. It reinforces the increasingly accepted view that vascular injury is a key component of serious COVID-19 illness. However, there remains much to learn about the interaction of the RAS, inflammation, and lung injury. Future mechanistic studies may do well to consider if accounting for the influence of sex can refine our understanding. However, perhaps most importantly, both animal and human COVID-19 studies must ensure equitable representation of the sexes to ensure that new insights benefit all patients without reinforcing preexisting disparities.

1 *Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA*

2 *Department of Medicine, Massachusetts General Hospital, Boston, MA*

3 *Department of Medicine, Division of Pulmonary, Allergy and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

The authors have disclosed that they do not have any potential conflicts of interest.

REFERENCES

1. Yeung ML, Teng JLL, Jia L, et al: Soluble ACE2-mediated cell entry of SARS-CoV-2 via interaction with proteins related to the renin-angiotensin system. *Cell* 2021; 184:2212–2228.e12
2. Imai Y, Kuba K, Rao S, et al: Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; 436:112–116
3. Leisman DE, Mehta A, Thompson BT, et al: Alveolar, endothelial, and organ injury marker dynamics in severe COVID-19. *Am J Respir Crit Care Med* 2022; 205:507–519
4. Ozkan S, Cakmak F, Konukoglu D, et al: Efficacy of serum angiotensin II levels in prognosis of patients with coronavirus disease 2019. *Crit Care Med* 2021; 49:e613–e623
5. Akin S, Schriek P, van Nieuwkoop C, et al: A low aldosterone/renin ratio and high soluble ACE2 associate with COVID-19 severity. *J Hypertens* 2022; 40:606–614
6. Leisman DE, Mastroianni F, Fisler G, et al: Physiologic Response to angiotensin II treatment for coronavirus disease 2019-induced vasodilatory shock: A retrospective matched cohort Study. *Crit Care Explor* 2020; 2:e0230
7. Cohen JB, Hanff TC, William P, et al: Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: A prospective, randomised, open-label trial. *Lancet Respir Med* 2021; 9:275–284
8. Puskarich MA, Ingraham NE, Merck LH, et al; Angiotensin Receptor Blocker Based Lung Protective Strategies for Inpatients With COVID-19 (ALPS-IP) Investigators: Efficacy of losartan in hospitalized patients with COVID-19-induced lung injury: A randomized clinical trial. *JAMA Netw Open* 2022; 5:e222735
9. Rocheleau GLY, Lee T, Mohammed Y, et al; ARBs CORONA I Investigators: Renin-Angiotensin System Pathway Therapeutics Associated With Improved Outcomes in Males Hospitalized With COVID-19. *Crit Care Med.* 2022; 50:1306–1317
10. Rabi DM, Khan N, Vallee M, et al: Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy. *Can J Cardiol* 2008; 24:491–496
11. Nukiwa T, Matsuoka R, Takagi H, et al: Responses of serum and lung angiotensin-converting enzyme activities in the early phase of pulmonary damage induced by oleic acid in dogs. *Am Rev Respir Dis* 1982; 126:1080–1086
12. Rouleau JL, Warnica WJ, Baillot R, et al; IMAGINE (Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme) Investigators: Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. *Circulation* 2008; 117:24–31
13. Prakash VS, Mansukhani NA, Helenowski IB, et al: Sex bias in interventional clinical trials. *J Womens Health (Larchmt)* 2018; 27:1342–1348
14. Horby P, White NJ, Landray MJ: Hydroxychloroquine in hospitalized patients with Covid-19. Reply. *N Engl J Med* 2021; 384:882