ACEing COVID-19: A Role For Angiotensin Axis Inhibition in SARS-CoV-2 infection?

Venkatesh L. Murthy, Mika Koupenova, Ravi Shah

[1]Department of Medicine and Radiology, University of Michigan, Ann Arbor, MI; [2]Department of Medicine, University of Massachusetts Medical School, Worcester, MA; [3]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, MA

American Heart Association.

Circulation Research

Subject Terms:
ACE/Angiotension Receptors/Renin Angiotensin System
Hypertension

Keywords:
Infection, hypertension, COVID-19.

Address correspondence to:
Dr. Ravi V. Shah
Assistant Professor of Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, MA 02114
Tel: 617-726-2000
rvshah@partners.org

DOI: 10.1161/CIRCRESAHA.120.317174

There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance. – Hippocrates[1]

Cardiometabolic disease, especially hypertension, is a common risk factor for mortality among individuals with SARS-CoV-2 disease (COVID-19). The role of hypertension and vascular disease in COVID-19 has raised considerable debate around how to best manage anti-hypertensive therapy to alter disease trajectory[2-5]. Given the role of the ACE2 receptor in SARS-CoV-2 viral entry[6], angiotensin system modulation by ACE inhibitors (ACE-I) or angiotensin-II receptor blockers (ARBs) in clinical management have taken center stage in this controversy. ACE2 is a carboxypeptidase that processes angiotensin-II to the angiotensin(1-7) fragment, a vasodilatory, anti-inflammatory peptide, which is hypothesized to reduce downstream angiotensin-II signaling and subsequent organ injury. Clinical ACE-I/ARBs do not directly block ACE2, and their effect on the regulation of ACE2 in model systems is mixed and appears context- and even tissue-dependent[7-9]. Nevertheless, the distribution of ACE2 expressed in type II alveolar cells in the lung and vascular endothelium more generally[10]—in conjunction with some reports in support of higher ACE2 expression after drug exposure—have raised the hypothesis that ACE-I/ARB therapy may facilitate SARS-CoV-2 entry and severe COVID-19.

In this issue of *Circulation Research*[15], Zhang *et al.* present retrospective observational data from >3000 individuals (including 1128 patients with hypertension) with COVID-19 in Hubei, China, to start to address this important clinical concern. COVID-19 diagnosis was secured by chest computed tomographic findings or PCR-based confirmation, and patients with severe acute or chronic clinical conditions apart from COVID-19 were excluded. Of note, individuals who discontinued treatment for hypertension were not excluded. The primary outcome was 28-day all-cause mortality. Consistent with prior reports, hypertension was associated with greater severity of illness and poorer outcomes. Given the retrospective observational design, propensity score-based matching was performed on an array of potential confounders related to ACE-I/ARB exposure, including age, sex, systemic inflammatory markers, and selected comorbid illness. In both unmatched and propensity matched cohort regressions with adjustment, the investigators observed that a prior or concurrent exposure to ACE-I/ARB was associated with a lower hazard of the primary outcome. In addition, in the propensity matched subsample of individuals on any hypertensive therapy, ACE-I/ARB had a similar association.

While these investigators are to be congratulated for this study and the care of COVID-19 patients, their conclusions have to be viewed in the context of a retrospective observational design. Statistical considerations include the use of a single method for propensity matching, residual confounding by unknown confounders or mediators (e.g., circulating ACE2 levels) or by features still different between ACE-I/ARB and non-ACEI/ARB groups (e.g., D-dimer, lipid lowering therapies, other anti-hypertensives), selection biases in terms of region and penetrance of different types of anti-hypertensive therapy, and difficulties in handling individuals who ceased therapy in hospital for worsening illness. Duration of antecedent ACE-I/ARB therapy may impact degree of ACE2 induction. Moreover, the time on ACE-I/ARB therapy during hospitalization (and better characterization of those individuals forced toward discontinuation for worsening disease severity) are likely critical factors. It is important to note that, while the investigators used standard techniques to attempt to reduce bias in this observational study via propensity matching, it is not a randomized study and the residual confounding inherent to this approach renders the conclusions hypothesis-generating at best.

With these caveats in mind, why might angiotensin system blockade with ACE-I/ARB be "protective" (or at least not necessarily harmful)? Certainly, for both SARS-CoV-1 and SARS-CoV-2, ACE2—potentially upregulated in target organs by ACE-I/ARB—is requisite for viral entry. Strikingly, after SARS-CoV-1 viral entry, the virus reduces cellular ACE2 expression, with subsequent lung injury dependent on the presence of ACE2[11]. Reduced ACE2 expression has been associated with increased pulmonary inflammation[12], with complete abrogation of ACE2 (and subsequent higher circulating angiotensin-II)

associated with lung injury in an avian influenza model[13]. This physiology is mirrored in myocardial tissue: infection with SARS-CoV-1 in mice reduces myocardial ACE2 expression, and patients with SARS-CoV-1 in the heart exhibit increased myocardial inflammation in conjunction with lower ACE2 expression[14]. These observations have been clear since the first SARS crisis and have renewed interest in clinical studies of angiotensin system modulation in COVID-19 via recombinant ACE2 administration (clinicaltrials.gov identifier NCT04287686) and randomized studies examining the role of losartan in COVID-19 (NCT04312009, NCT04311177).

Needless to say, these studies (and others with appropriate randomization and controls) are sorely needed to offer our patients relief from COVID-19. The current pandemic, however, has forced a nimble response to guide therapeutic decisions in the immediate term. How do we interpret the findings of Zhang *et al.* in this context? The conclusions of this study should not be taken as a surrogate for appropriate randomized data guiding the clinical management of individuals on ACE-I/ARB with COVID-19. While we cannot conclude from this data anything on the pathophysiologic/mechanistic role of ACE-I/ARB during COVID-19, it offers retrospective, observational support to ongoing randomized controlled studies of these medications in the fight against COVID-19. Currently, outside of clear clinical indications to stop these medications that have existed long before the current pandemic (e.g., expected or concurrent worsening renal failure, hyperkalemia, hypotension, etc.), the withdrawal of these medications in the context of those conditions in which they have a proven benefit (e.g., heart failure with reduced left ventricular ejection fraction) may actually inflict more harm than good. In the end, we must rely on randomized clinical science for the benefit of our patients, and the study of Zhang and colleagues is a directed step toward that goal.

DISCLOSURES

Dr. Murthy owns stock in General Electric and Cardinal Health and stock options in Ionetix. He has received research grants and speaking honoraria from Siemens Medical Imaging and expert testimony fees on behalf of Jubilant Draximage. He has served on medical advisory boards for Ionetix and Curium. Dr. Murthy and Dr. Shah are supported in part by grants from the National Institutes of Health and the American Heart Association. Dr. Shah has served as a consultant in the past 12 months for Myokardia (ongoing) and Best Doctors (ongoing) and has minor stock holdings in Gilead. Dr. Shah is a co-inventor on a patent for ex-RNAs signatures of cardiac remodeling. Dr. Murthy is supported in part by the Melvyn Rubenfire Endowed Professorship.

REFERENCES

1. https://www.goodreads.com/quotes/4117-there-are-in-fact-two-things-science-and-opinion-the. Accessed 16 April 2020.
2. Fang L, Karakiulakis G and Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8:e21.
3. European Societies of Cardiology. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed 16 April 2020.
4. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19. Accessed 16 April 2020.
5. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, Widmer AF and Osswald S. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J*. 2020.

6. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C and Pohlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020.
7. Hamming I, van Goor H, Turner AJ, Rushworth CA, Michaud AA, Corvol P and Navis G. Differential regulation of renal angiotensin-converting enzyme (ACE) and ACE2 during ACE inhibition and dietary sodium restriction in healthy rats. *Exp Physiol*. 2008;93:631-8.
8. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI and Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;111:2605-10.
9. Ocaranza MP, Godoy I, Jalil JE, Varas M, Collantes P, Pinto M, Roman M, Ramirez C, Copaja M, Diaz-Araya G, Castro P and Lavandero S. Enalapril attenuates downregulation of Angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. *Hypertension*. 2006;48:572-8.
10. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G and van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631-7.
11. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C and Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875-9.
12. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, McCray PB, Jr., Chappell M, Hackam DJ and Jia H. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg(9) bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *Am J Physiol Lung Cell Mol Physiol*. 2018;314:L17-L31.
13. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, Ju X, Liang Z, Liu Q, Zhao Y, Guo F, Bai T, Han Z, Zhu J, Zhou H, Huang F, Li C, Lu H, Li N, Li D, Jin N, Penninger JM and Jiang C. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. *Nat Commun*. 2014;5:3594.
14. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM and Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest*. 2009;39:618-25.
15. Zhang P, Zhu L, Cai J, Lei F, Qin KK, Xie J, Liu Y-M, Zhao Y-C, Huang, X, Lin L, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020: xxx-xxx.