ESC European Society of Cardiology
European Heart Journal (2020) **41**, 2126–2127
doi:10.1093/eurheartj/ehaa423

Renin–angiotensin–aldosterone system dysregulation and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

Thadathilankal-Jess John [1]* and Kiran John[2]

[1]Division of Cardiology, Department of Medicine, Stellenbosch University & Tygerberg Academic Hospital, Cape Town, South Africa; and [2]Division of General Internal Medicine, Department of Medicine, Stellenbosch University & Tygerberg Academic Hospital, Cape Town, South Africa

Online publish-ahead-of-print 20 May 2020

This commentary refers to 'SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19?', by G.M. Kuster et al., doi: 10.1093/eurheartj/ehaa235.

Since the identification of the novel SARS-CoV-2 virus, there has been significant interest regarding the possibility of antihypertensives, specifically angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), increasing mortality in patients infected with SARS-CoV-2. This has been driven by various studies demonstrating an increase in angiotensin-converting enzyme 2 (ACE2) levels in patients using ACE-Is and ARBs. The article by Kuster *et al.* highlights how increased ACE2 expression may not necessarily translate to an increase in the coronavirus viral load. Moreover, it is also not known whether an increased viral load necessarily suggests increased disease severity.[1]

Mortality with the SARS-CoV-2 appears to be driven by the development of acute lung injury and acute respiratory distress syndrome (ARDS) due to an underlying cytokine storm. Previous work has suggested a significant role of the renin–angiotensin–aldosterone system (RAAS) in the development of ARDS. ARDS may be linked to an up-regulation of the vasoconstrictive, fibroproliferative, and proinflammatory effects of an ACE/angiotensin II (ATII) pathway and the down-regulation of the vasodilatory, anti-inflammatory, and antifibrotic properties of an ACE2/angiotensin 1-7 (product of the breakdown of ATII by ACE2) pathway.[2–4]

The protective role of the ACE2 pathway in various viral pneumonias has been supported by other studies in both animal and human models.[3] The deleterious role of the angiotensin II signalling pathway in the current SARS-CoV-2 outbreak is supported by a report of a group of 12 cases of SARS-CoV-2-infected patients where ATII levels in the plasma were increased and linearly associated with the severity of lung injury.[5]

We suggest that ACE-Is and ARBs may in fact play a protective role in reducing the degree of lung injury in SARS-CoV-2 by shifting the RAAS system from an ACE/ATII pathway to an ACE2/angiotensin 1-7 signalling pathway.

ACE-Is reduce the conversion of angiotensin I (ATI) to ATII, preventing the deleterious aforementioned effects. In addition, it has been identified that ATII may stimulate interleukin-6 (IL-6) release via an NF-κB-dependent pathway mediated predominantly by binding of ATII to the angiotensin II type 1 receptor subtype (AT1R).[4] Reduced levels of ATII (with ACE-I use) may thus also dampen the cytokine storm syndrome which is typical of severe SARS-CoV-2 infection.

During a basal RAAS state, AT1Rs form complexes with ACE2 on the surface of cell membranes. In a stimulated RAAS state (as with SARS-CoV-2 infection), with increased levels of ATII present, there is reduced interaction between AT1Rs and ACE2 with resultant ubiquitination and ACE2 internalization.[3] AT1R-specific ARBs, by predominantly blocking ATII binding of AT1Rs, will (i) reduce the vasoconstrictive effects of ATII; (ii) reduce the release of IL-6 and other proinflammatory cytokines; and (iii) reduce the internalization of the protective ACE2. In addition, binding of ATII to the free angiotensin II type 2 receptors (AT2R) will typically have largely opposite effects to binding to AT1R with a vasodilatory, anti-inflammatory, and antifibrotic effect.

We therefore add further data to support the suggestions of Kuster *et al.* that the increased signal for mortality in patients with hypertension, diabetes, and cardiovascular disease may suggest a

* Corresponding author. Division of Cardiology, Department of Medicine, Stellenbosch University & Tygerberg Academic Hospital, PO Box 241, Cape Town, 8000, South Africa. Tel: +27 767702123, Email: jessjohnt@gmail.com

high-risk population as well as a group of individuals with a dysregulated RAAS in favour of an ACE/angiotensin II signalling pathway.

Conflict of interest: none declared.

References

1. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, Widmer AF, Osswald S. SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 2020;doi: 10.1093/eurheartj/ehaa235.
2. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Crit Care* 2017;**21**:234.
3. Sparks M, Hiremath, S. *The Coronavirus Conundrum: ACE2 and Hypertension*. http://www.nephjc.com/news/covidace2 (18 March 2020).
4. Skurk T, Van Harmelen V, Hauner H. Angiotensin II stimulates the release of interleukin-6 and interleukin-8 from cultured human adipocytes by activation of NF-κB. *Arterioscler Thromb Vasc Biol* 2004;**24**:1199–1203.
5. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;**63**:364–374.