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Potential benefit of angiotensin II in COVID-19 patients: beyond reasonable doubt?

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We read with great interest the editorial by Busse et al. on the potential use of angiotensin II in the treatment of COVID-19 [1]. However, amidst the myriad of attempted interventions, some may be more reasonable than others [2].

In preclinical studies, SARS-CoV-1-mediated ACE-2 downregulation led to increased lung injury [3]. The extrapolated protective role of ACE2 in human lung infections seems to result from both the breakdown of angiotensin II and the generation of Ang1–7 and Ang1–9, anti-inflammatory, antioxidative, and antiproliferative peptides that thwart the detrimental effects of angiotensin II in lung parenchyma [3]. Notably, angiotensin II receptor I blockade salvaged a rodent model from more profound alveolar damage [3]. In a clinical setting, recombinant human ACE2 significantly reduced angiotensin II and hinted towards lower mortality in a small randomized trial of undifferentiated ARDS patients [4]. Taken together, these studies cast little doubt on the true colors of angiotensin II during severe COVID-19 pneumonia. Conversely, observational data have revealed no harm and even disclosed potential benefit associated with RAAS modulation [5]. Hence, the assumption of Busse et al. is frankly counterintuitive. Ongoing RCTs evaluating rhACE2 (NCT04335136), AT-1 receptor blockade (NCT04312009), and ACEi/ARB continuation or discontinuation after COVID-19 diagnosis (NCT04329195) are eagerly expected to shed more light into present uncertainties.

Busse et al. advocate for the compassionate use of angiotensin II in critically ill patients with supervening shock and suggest it may even be used prophylactically. In an aged population with cardiovascular comorbidities, in which RAAS blockade has earned a pivotal protective role for decades, such radical shift could have additional unforeseen consequences. Angiotensin II effectively increased blood pressure on top of norepinephrine in the ATHOS-3 trial. Although certainly appealing and offering an alternative pathway to improve mean arterial pressure and organ perfusion in vasodilatory shock, more limb ischemia and de novo infections were also noted, raising safety concerns. In severe COVID-19 patients, in whom the percentage of refractory shock in unclear, the utility of a second vasopressor seems even more unwarranted.

From our perspective, it appears unlikely and even paradoxical to anticipate a net clinical benefit of angiotensin II in COVID-19. If reasonable doubt still persists, this assumption should be put to the test like other putative beneficial interventions [2]. Beyond their individual plausibility, all proposed therapies in COVID-19 patients should be considered experimental and cannot be universally recommended until evaluated in properly conducted RCTs.

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Authors' response

Angiotensin II for COVID-19-induced shock: beyond a reasonable doubt, an ACE in the hole

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We thank Tralhão et al. for bringing up important issues regarding our commentary on the use of angiotensin II for vasodilatory shock in COVID-19 patients. Given recent data to support continuing ACE-inhibition in patients with COVID-19, we are not arguing to cease such therapy in hemodynamically stable patients. However, those with vasodilatory shock are clearly not the same as those on ACE-inhibitors, and the "pivotal protective role" of RAAS blockade has been associated with increased risk of hemodynamic compromise in critically ill patients [6]. We also caution against an argument based on the pilot study by Khan et al. of recombinant human ACE2 for patients with ARDS, which was halted due to clinical futility and relies only on angiotensin II levels, rather than the ratio of angiotensin II to angiotensin I, which may have greater clinical relevance [7, 8].

Dr. Tralhão's argument that lung injury results directly from increased angiotensin II levels due to virally mediated downregulation of ACE-2 rather than from direct viral invasion not only ignores basic human physiology but also runs contrary to the currently available evidence. Had increased levels of angiotensin II been detrimental to lung parenchyma, this would have been suggested by the results of ATHOS-3, which showed no such effect [9]. Further data support the safety of angiotensin II in patients with COVID-19. Zangrillo et al. recently reported using angiotensin II for COVID-19-induced vasodilatory shock in 16 patients, 10 of whom received it as a first-line and only requisite vasopressor [10]. Contrary to concerns expressed by Tralhão et al., patients treated with angiotensin II had significant *improvements* in FiO_2 (0.70 to 0.40), PEEP (14 to 11 cmH_2O), and SpO_2/FiO_2 ratio (121.4 to 200.0) at 48 h. Despite staggeringly high global mortality rates for COVID-19-induced vasodilatory shock, 14 of the 16 patients in this case series were alive at the time of the authors' submission of their report.

Cognizant of the dilemma of having to manage critically ill patients in the absence of disease-specific data, we must continue to rely on tangentially-related, randomized controlled trials like ATHOS-3, as well as convincing clinical experience, as provided by Zangrillo et al. We fully support Dr. Tralhão's suggestion that well-designed studies should inform our treatment options. While some clinicians may lack clinical equipoise regarding angiotensin II, we still maintain that it should be evaluated in the setting of COVID-19, based on a rational physiological argument and emerging supportive data.

Abbreviations

ACE: Angiotensin converting enzyme; ACE2: Angiotensin converting enzyme 2; ACEi: Angiotensin converting enzyme inhibitors; Ang: Angiotensin; ARB: Angiotensin receptor blocker; ARDS: Acute respiratory distress syndrome; AT-1: Angiotensin II receptor I; RAAS: Renin angiotensin aldosterone system; RhACE2: Recombinant human angiotensin converting enzyme 2; RCT: Randomized clinical trial; SARS-Cov-1: Severe acute respiratory syndrome coronavirus 1

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AT wrote the first version of the manuscript. LFM and PP revised the manuscript for important intelectual content. All authors read and approved the final manuscript.

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References

1. Busse LW, Chow JH, McCurdy MT, Khanna AK. COVID-19 and the RAAS - a potential role for angiotensin II? Crit Care. 2020;24:1–4.
2. Kalil AC. Treating COVID-19. Off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA. 2020. https://doi.org/10.1001/jama.2020.4742.
3. Kuba K, Imai Y, Rao S, Jiang C, Penninger JM. Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. J Mol Med. 2006;84:814–20.
4. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017;21:1–9.
5. Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino RB, Harrington DP. Inhibitors of the renin–angiotensin–aldosterone system and Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMe2012924.
6. Dial S, Nessim SJ, Kezouh A, Benisty J, Suissa S. Antihypertensive agents acting on the renin-angiotensin system and the risk of sepsis. Br J Clin Pharmacol. 2014;78(5):1151–8.

7. Khan A, Benthin C, Zeno B, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017;21:234.
8. Bellomo R, Wunderink RW, Szerlip H, et al. Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. Crit Care. 2020;24:43.
9. Busse LW, Albertson TE, Gong MN, et al. Outcomes in patients with acute respiratory distress syndrome receiving angiotensin II for vasodilatory shock [abstract P125]. Crit Care. 2018;22(suppl 1):82 (50).
10. Zangrillo A, Landoni G, Beretta L, Morselli F, Serpa Neto A, Bellomo R, COVID-BioB Study Group. Angiotensin II infusion in COVID-19-associated vasodilatory shock: a case series. Crit Care. 2020;24:227.

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