

LETTER

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Treatment with angiotensin II in COVID-19 patients may not be beneficial



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Dear Editor,

We read with great interest the recent article by Zangrillo et al. regarding infusion of angiotensin II (ANGII) in COVID-19 [1], stating that ANGI vasopressor treatment may be logical in the setting of COVID-19 patients requiring vasopressor support. The authors refer to the ATHOSIII trial as support for the use of ANGI in catecholamine-resistant vasodilatory shock despite the known concern for thrombotic and infectious complications associated with ANGI [2]. In addition, the authors suggest to use ANGI in COVID-19 patients recently exposed to angiotensin-converting enzyme inhibitors. We believe that both these statements raise some concern.

SARS-CoV-1 downregulates ACE2 with a subsequent increase in ANGI levels creating a disruption akin to over activating the renin-angiotensin-aldosterone system (RAAS) [3]. In a recent COVID-19 case series, ANGI

levels were markedly elevated and linearly associated with viral load and lung injury [4]. Moreover, in a prepublished report currently under journal review, infusion of ANGI in a porcine model rapidly (within hours) induced a clinical syndrome closely reflecting the one seen in COVID-19 patients, including histological changes in the lungs with severe thickening of the alveolar walls, possible hyaline membranes, and clotting of vessels, as previously reported in the human COVID-19 phenotype [5].

We suggest that much of the pathophysiology in ICU patients with COVID-19 is potentially driven by a loss of the inhibition of the RAAS, causing supranormal concentrations of ANGI [5]. In our opinion, the use of ANGI in COVID-19 patients is therefore at present most questionable. Rather, we propose further evaluation of a plausible contributing mechanism of RAAS behind pathophysiology seen in COVID-19.

Authors' response

Alberto Zangrillo, Giovanni Landoni, Luigi Beretta, Federica Morselli, Ary Serpa Neto and Rinaldo Bellomo

We thank Dr. Rysz and colleagues for their correspondence [6].

In response, we note that their concerns about the increased risk of thrombosis and infection with angiotensin II have no statistical substance. In addition, for objectivity, other adverse effects would also have to be

similarly considered, such as a 34% reduction in adverse effects leading to discontinuation compared to placebo, or the 34% reduction in respiratory adverse events, or the absolute 6.4% reduction in serious adverse events compared to placebo [7].

The endocytosis of ACE2 following contact with the COVID-19 virus could be decreased by conformational changes in ACE2 secondary to angiotensin II binding to it. In addition, such binding could itself decrease the ability of the virus to bind to the receptor and enter the cell. Such hypothetical interactions, however, remain unmeasured. Moreover, it is not a surprise that angiotensin II levels are higher in patients with greater

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viral load and illness severity. Such high levels can easily represent the response to inflammatory vasodilatation and the body's attempt to restore perfusion pressure.

Finally, the infusion of angiotensin II in the porcine model cited by the correspondents is clearly irrelevant to angiotensin therapy in humans as described in our report [1]. We administered 20 ng/kg/min [1], while the investigators escalated to 80 ng/kg/min within 60 min and then all the way to 240 ng/kg/min. In other animals, the dose was up to 640 ng/kg/min. At such toxic doses which were 10 to 30 times those administered to our patients, it is no surprise that toxic, even lethal side effects developed.

Until more relevant experiments are performed or clear evidence emerges that angiotensin II infusion is injurious in COVID-19 patients, the data are strong that angiotensin II is a safe and effective vasopressor agent [8] especially in patients with high renin levels [9].

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Authors' contributions

SR, JL, and MJF drafted the paper. All authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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