generally considered to be a pure vasopressor devoid of a direct inotropic effect. Nonetheless, whether angiotensin II exerts an inotropic effect could be dependent on the type of aggression and basal cardiac function, as well as on the endogenous concentration of angiotensin II, and deserves further explorations in animal models and patients.

In conclusion, this additional hypothesis gives a glimpse into the complex picture of the RAAS perturbations during shock (Figure 1), emphasizes the need for further research in this area, and expands the spectrum of potential therapeutic targets. ■

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References

1. Bellomo R, Forni LG, Busse LW, McCurdy MT, Ham KR, Boldt DW, *et al*. Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock: a clinical trial. *Am J Respir Crit Care Med* 2020;202:1253–1261.
2. Bellomo R, Wunderink RG, Szerlip H, English SW, Busse LW, Deane AM, *et al*. Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. *Crit Care* 2020; 24:43.
3. Rehfeld L, Funk E, Jha S, Macheroux P, Melander O, Bergmann A. Novel methods for the quantification of dipeptidyl peptidase 3 (DPP3) concentration and activity in human blood samples. *J Appl Lab Med* 2019;3:943–953.
4. Prajapati SC, Chauhan SS. Dipeptidyl peptidase III: a multifaceted oligopeptide N-end cutter. *FEBS J* 2011;278:3256–3276.
5. Deniau B, Rehfeld L, Santos K, Dienelt A, Azibani F, Sadoune M, *et al*. Circulating dipeptidyl peptidase 3 is a myocardial depressant factor: dipeptidyl peptidase 3 inhibition rapidly and sustainably improves haemodynamics. *Eur J Heart Fail* 2020;22:290–299.
6. Jha S, Taschler U, Domenig O, Poglitsch M, Bourgeois B, Pollheimer M, *et al*. Dipeptidyl peptidase 3 modulates the renin-angiotensin system in mice. *J Biol Chem* 2020;295:13711–13723.
7. Deniau B, Blet A, Santos K, Vaittinada Ayar P, Genest M, Kästorf M, *et al*. Inhibition of circulating dipeptidyl-peptidase 3 restores cardiac function in a sepsis-induced model in rats: a proof of concept study. *PLoS One* 2020;15:e0238039.
8. Leisman DE, Fernandes TD, Bijol V, Abraham MN, Lehman JR, Taylor MD, *et al*. Impaired angiotensin II type 1 receptor signaling contributes to sepsis induced acute kidney injury. *Kidney Int* [online ahead of print] 31 Aug 2020; DOI: 10.1016/j.kint.2020.07.047.

Reply to Picod *et al.*

From the Authors:

We thank Picod and colleagues for their comments about our manuscript (1). The renin–angiotensin–aldosterone system (RAAS) is disordered in patients with catecholamine-resistant vasodilatory shock (CRVS). Thus, we have described the RAAS Disturbance Hypothesis, which postulates that there is inadequate activation of the ATR1 (angiotensin type I receptor) in some patients with CRVS. In our study, we demonstrated that elevated renin levels are common in patients with CRVS and that the renin levels correlate with the angiotensin I/angiotensin II ratio, which is also elevated (1). We reasoned that ACE (angiotensin-converting enzyme) dysfunction was the most likely cause for these findings. This hypothesis is bolstered by our findings that the exogenous administration of angiotensin II resulted in a rapid decrease in both renin and angiotensin I levels compared with placebo. Picod and colleagues rightly point out that increased angiotensin II degradation by neutral endopeptidase offers an additional explanation for our findings. We agree that this is important and that further research into the nature and cause of angiotensin II insufficiency and the role of both classical and nonclassical enzymes (ACE, ACE2, and/or neutral endopeptidase) in the generation and degradation of the different major angiotensins identified so far (especially angiotensin I, angiotensin II, angiotensin 1-7, angiotensin 1-9, and angiotensin 15) is warranted.

The consequences of RAAS disturbance in CRVS are broad and impact multiple organs. Preclinical studies confirm early findings by Wan and colleagues that adequate ATR1 engagement is critical for renal function (2). Recently, Leisman and colleagues demonstrated

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that impaired ATR1 signaling contributes to sepsis-induced acute kidney injury (AKI) (3). In this study, administration of angiotensin II was found to attenuate AKI whereas the administration of losartan exacerbated AKI. The focus on renal function is obvious, but the ATR1 receptor also has important cardiac function. The ATR1 receptor has dual signaling via G protein–coupled receptor and the β-arrestin pathway. In addition, β-arrestin modulates internalization of the receptor and the inotropic properties of angiotensin II (4, 5).

In summary, at a clinical level, RAAS disturbances in CRVS may be identified by serum renin measurement, which is an inexpensive and widely available test. Elevated renin levels may represent a bio-type of CRVS, which can be treated with RAAS-modulating agents to improve patient-centered outcomes including survival. At a biological level, the journey to understand the extraordinary complexity of the nonclassical RAAS pathways has just begun. ■

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References

1. Bellomo R, Forni LG, Busse LW, McCurdy MT, Ham KR, Boldt DW, *et al*. Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock. A clinical trial. *Am J Respir Crit Care Med* 2020;202:1253–1261.
2. Wan L, Langenberg C, Bellomo R, May CN. Angiotensin II in experimental hyperdynamic sepsis. *Crit Care* 2009;13:R190.
3. Leisman DE, Fernandes TD, Bijol V, Abraham MN, Lehman JR, Taylor MD, *et al*. Impaired angiotensin II type 1 receptor signaling contributes to sepsis induced acute kidney injury. *Kidney Int* [online ahead of print] 31 Aug 2020; DOI: 10.1016/j.kint.2020.07.047.
4. Hunyady L. Molecular mechanisms of angiotensin II receptor internalization. *J Am Soc Nephrol* 1999;S47–S56.
5. Rajagopal K, Whalen EJ, Violin JD, Stiber JA, Rosenberg PB, Premont RT, *et al*. β-arrestin2-mediated inotropic effects of the angiotensin II type 1A receptor in isolated cardiac myocytes. *Proc Natl Acad Sci USA* 2006;103:16284–16289.