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Alteration of the Renin–Angiotensin–Aldosterone System in Shock: Role of the Dipeptidyl Peptidase 3

To the Editor:

We read with interest the article published by Bellomo and colleagues, which explored some of the alterations of the renin–angiotensin–aldosterone system (RAAS) during catecholamine-resistant vasodilatory shock, mostly of septic origin, using data from the ATHOS-3 (Phase 3 Angiotensin II for the Treatment of High-Ouptut Shock) trial (1). In this work, the authors demonstrated that there was increased renin concentration in most patients, which was associated with a high angiotensin I/angiotensin II ratio and a bad prognosis (2). As the latter ratio is inversely associated with ACE (angiotensin-converting enzyme) activity, the authors suggest that RAAS perturbations might be related to a decrease in ACE activity in the context of sepsis-associated endotheliopathy. We would like to propose another, coexisting rather than competing, hypothesis of the RAAS perturbation observed during septic shock. As highlighted by Bellomo and colleagues (1), insufficient activation of the AT1R (angiotensin II type 1 receptor) can be caused by AT1R blockade or decreased angiotensin II generation by ACE. On the basis of recent discoveries, we propose enhanced degradation of angiotensin II as a third possibility related to an excess release of DPP3 (dipeptidyl peptidase 3) in the plasma of patients with septic shock (3).

DPP3 is a zinc-dependent metalloprotease that cleaves the N-terminal extremity of various bioactive peptides, including angiotensins, enkephalins, and endorphins (4). Interestingly, although DPP3 hydrolyzes angiotensin II into angiotensin IV, it has no direct effect on angiotensin I, thus leading to an increased angiotensin I/angiotensin II ratio, consistent with Bellomo and colleagues' findings (5, 6). Under these conditions, as pointed out by the authors, decreased AT1R stimulation then triggers the production of renin.

Although the plasmatic concentration of DPP3 is low in healthy subjects, an increase in plasmatic DPP3 concentration and activity has been observed in patients with sepsis. In addition, DPP3 activity is higher in septic shock than in severe sepsis and higher in decedents than in survivors of septic shock (3). In a rat model of septic shock with septic cardiomyopathy induced by cecal ligation and puncture, circulating DPP3 activity is also increased (7). Furthermore, in this preclinical model, inhibition of DPP3 activity with procizumab (α-DPP3 monoclonal antibody) quickly restored cardiac function as measured by left ventricular shortening fraction and improved survival (7). However, the exact mechanism behind the beneficial hemodynamic effect of DPP3 inhibition remains to be identified.

Notably, and despite some substantial biological rationale, it remains uncertain whether angiotensin II infusion alone is able to recapitulate the beneficial effects of DPP3 inhibition. Indeed, although this therapy has been associated with an AT1R-dependent increment of cardiac output in a mouse model of sepsis (8), this is a rather inconstant finding in humans, in whom angiotensin II is

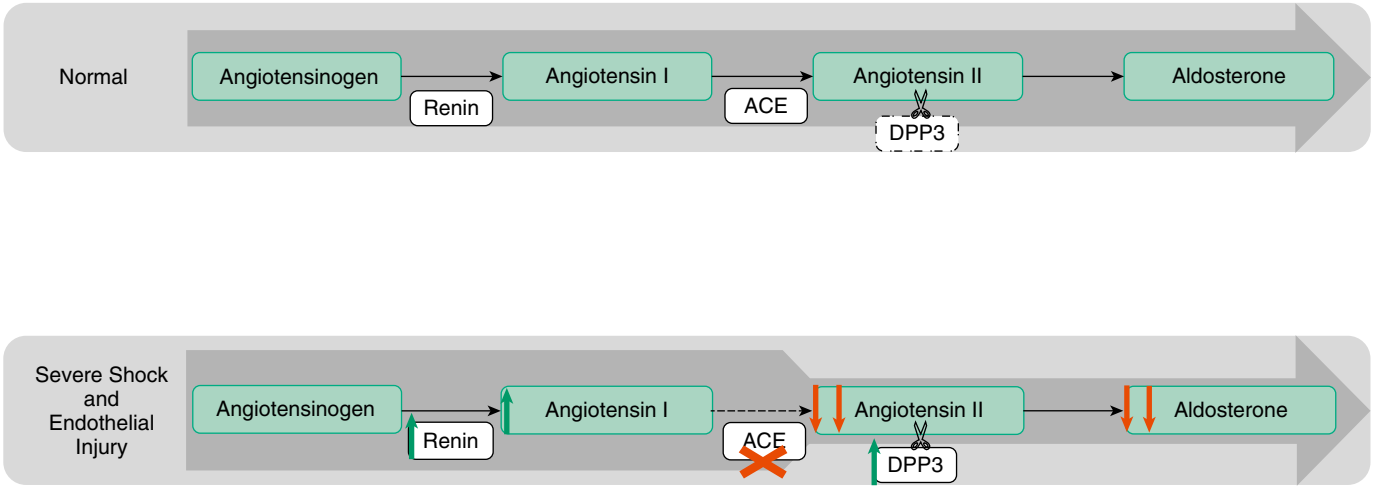

Figure 1. An alternative renin–angiotensin–aldosterone system–disturbance hypothesis. Adapted from Reference 1. ACE = angiotensin-converting enzyme; DPP3 = dipeptidyl peptidase 3. Green arrows: increased concentration. Red arrows: decreased concentration. Red X: insufficient activity.

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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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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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