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Reply to Weatherald *et al.*

From the Authors:

We thank Weatherald and colleagues for their supportive comments, and pleasant reminiscence of French cuisine, on our recent report on risk reduction and hemodynamics after initial dual combination of therapies in pulmonary arterial hypertension (1). We fully agree on the importance of pulmonary vascular resistance combined with imaging of the right heart, as there may be dissociation (2), although this is unlikely when pulmonary vascular resistance decreases by more than 50–60% (3). Their other points are also well taken. *1*) Redundancies in pulmonary arterial hypertension risk scores easily occur, as most parameters of prognostic relevance are inevitably related to right ventricular function. We could indeed have acknowledged this with greater clarity. *2*) Sex differences in risk scores are of great clinical relevance in relation to the greater capacity of the female right ventricle to adapt to increased afterload, as recently reemphasized (4). *3*) The inevitable failure of initial dual-combination therapy in high-risk patients strongly argues in favor of their treatment with initial triple-combination therapies.

We like to add that not only initial high-risk patients fail and that the definition of a high-risk status may vary greatly from one score to another. Over half of treated patients actually remain with poor prognosis intermediate or high-risk status whatever the scoring system. This calls for earlier and more intensive combination therapies with parenteral prostanoids and more intensive follow-up with repetitive right heart catheterizations and imaging modalities (5). ■

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

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Originally Published in Press as DOI: 10.1164/rccm.202010-3834LE on October 26, 2020

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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

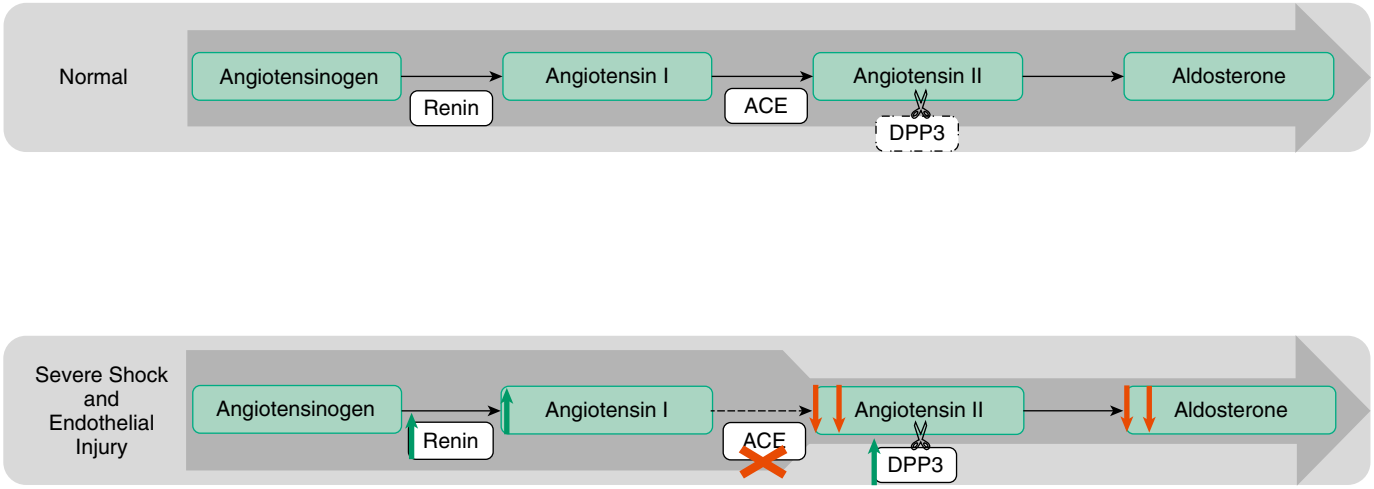

Figure 1. An alternative renin–angiotensin–aldosterone system–disturbance hypothesis. Adapted from Reference 1. ACE = angiotensin-converting enzyme; DPP3 = dipeptidyl peptidase 3. Green arrows: increased concentration. Red arrows: decreased concentration. Red X: insufficient activity.

The Cardiovascular Markers in Stress Conditions (MASCOT) Research Group is supported by an unrestricted research grant from 4TEEN4 Pharmaceuticals GmbH, which allowed salary support for one co-author (B.D.).

Originally Published in Press as DOI: 10.1164/rccm.202010-3873LE on November 5, 2020