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LETTER

Angiotensin-converting enzymes in acute respiratory distress syndrome

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Dear Editor,

Experimental studies have suggested that the activation of the pulmonary renin-angiotensin system (RAAS) may contribute to the development of acute respiratory distress syndrome (ARDS) by an increased vascular permeability, activation and alterations of alveolar epithelial cells [1, 2]. While the angiotensin-converting enzyme (ACE) mainly produces angiotensin II (Ang-II) and exerts vasoactive effects through AT1 and AT2 receptors, angiotensin-converting enzyme 2 (ACE2) produces Ang 1–7 from Ang II, which binds to a specific Mas receptor (MasR) and counterbalances the effects of the AT1 receptor activation. Data on the role of ACE2 in ARDS are very limited, although ACE2 activation protects mice from acute lung injury [3]; no human studies have assessed the role of ACE and ACE2 in patients with ARDS.

We prospectively studied the association of ACE, ACE2 and ACE/ACE2 with the severity and outcome of 96 adults (i.e., > 18 years of age) treated by mechanical ventilation for ARDS [4]. Written consent was obtained from patients' legal representatives. Plasma concentrations of ACE and ACE2 were measured by a quantitative ELISA method (Cloud-Clone Corp., Houston, TX, USA) at the time of ARDS recognition (T0) and on the following day (T1). Mortality was assessed at ICU discharge.

We found that at T1, but not at T0, plasma levels of ACE were significantly higher in non-survivors [$n = 32$; median 144 (103–254) ng/ml vs. median 112 (88–164), $p = 0.03$, Fig. 1] and in patients with poor composite outcome [i.e., mortality and/or duration of mechanical ventilation > 10 days, $n = 44$; median 136 (102–244) vs. 110 (83–155) ng/ml, $p = 0.02$] than others, whereas

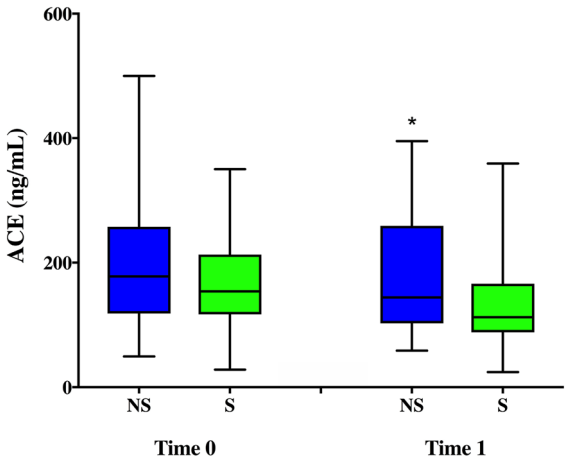

Fig. 1 Angiotensin-converting enzyme (ACE) levels at T0 and T1 according to ICU mortality (*NS* non-survivors; *S* survivors). *$p = 0.03$

no significant differences were found at any time point for ACE2 levels or the ACE/ACE2 ratio between groups (Supplemental Fig. 1). Also, ACE levels at T1 were higher in non-survivors than in survivors in the subgroups of patients on vasopressors [$n = 51$, 194 (117–273) vs. 116 (88–155) ng/ml, $p = 0.02$], with a SOFA score > 8 [$n = 51$, median 211 (120–273) vs. 118 (91–174) ng/ml, $p = 0.05$] or with a $PaO_2/FiO_2 < 100$ [$n = 15$, median 153 (117–273) vs. 120 (88–178) ng/ml, $p = 0.02$]. Other subgroup analyses are reported in the Supplemental Material. In a multivariable analysis, the plasma level of ACE at T1 remained independently associated with mortality [OR 1.008 (95% CIs = 1.001–1.015); $p = 0.03$, Supplemental Tables 1–2; Supplemental Fig. 3]. The receiver-operating characteristic area under the ROC curve for the ACE levels at T1 to predict ICU mortality was 0.64 (0.52–0.76; $p = 0.03$; Supplemental Fig. 2).

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Despite several limitations (Supplemental Material), these preliminary results underline the direct association between ACE plasma levels and poor outcome after ARDS. No impact of ACE2 concentrations on mortality was observed; however, these results may be explained by some difference between ACE2 levels and ACE2 activity in humans, as described in animal models [5]. Blood ACE concentration within the first 24 h may have prognostic implications.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05600-6) contains supplementary material, which is available to authorized users.

Compliance with ethical standards

Conflicts of interest
The authors declare they have no conflicts of interest related to this manuscript.

Ethical approval
The Institutional Ethics Committee approved the study (protocol number 2013/269).

Informed consent
Written informed consent was obtained from the patient or the patient's representative or next of kin.

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