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Increased levels of pro-AVP and pro-ADM in septic shock patients: what could it mean?

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Although the incidence of septic shock increases over years, its mortality rate remains unacceptable. During septic shock, severe alterations of the cardiovascular system participate in refractory hypotension and multi-organ failure, leading to death. Therefore, the measurement of biomarkers reflecting and/or involved in cardiovascular disturbances is highly attractive to better understand the mechanisms of septic shock, to stratify the risk of death and also to define future therapeutic targets.

Arginine vasopressin (AVP), a hormone synthesized in the hypothalamus, is released by increased plasma osmolality, decreased arterial pressure, and reductions in cardiac volume [1]. When released in the circulation, AVP contributes to fluid homeostasis and induces vasoconstriction. It is cosynthesized with pro-AVP (also known as copeptin), both derived from their larger precursor prepro-AVP. In human septic shock, a biphasic secretion pattern of AVP is observed, characterized by an initial increase followed by a decrease afterward [2, 3]. Moreover, as observed for other stress hormones like

cortisol, a relative AVP deficiency has been observed in late septic shock patients that could participate in hemodynamic failure and prognosis [2]. Therefore, although high levels of AVP or pro-AVP have been measured in infected patients [4, 5], it is still questioned whether high levels of these hormones or, at the opposite end, relatively low levels, are associated with prognosis during the course of septic shock. Adrenomedullin (ADM) is mainly released from endothelial cells. Unlike AVP, it notably exhibits vasodilation and natriuretic properties [6]. Although the secretion of ADM or its cosynthesized peptid pro-ADM is also increased during sepsis [7, 8], the mechanisms of their overproduction are unclear. Indeed, like other calcitonin peptides such as procalcitonin, ADM gene upregulation is also stimulated by bacterial endotoxins and pro-inflammatory cytokines [9]. AVP and ADM are supposed to have opposite mechanisms of secretion and opposite effects on hemodynamics. This reinforces the interest in studying their respective production kinetics in septic shock patients.

In this issue of Intensive Care Medicine, Dr. Guignant and coworkers [10] measured pro-AVP and pro-ADM levels during the first week of septic shock. Their 99 patients mainly presented with pulmonary or abdominal sepsis, and 28-day mortality was 35%. The measured levels of pro-AVP and pro-ADM appeared much higher than reported in healthy individuals. Although no control group has been studied, this result suggests an increased secretion of these markers in septic shock patients. Pro-AVP levels were the highest early after shock initiation with a decrease afterward. Pro-AVP levels were higher in non-survivors and exhibited the best prognostic value at day 1–2 and at day 3–4 of shock. Later, pro-AVP levels were not very different between survivors and non-survivors, which could reflect a secondary AVP deficiency in the latter, as suggested by other authors [2, 11]. Pro-ADM levels were also higher in non-survivors, but the prognostic value of this marker increased with time,

unlike for pro-AVP. Future works should clarify whether the relative increase of pro-ADM with time in non-survivors results from an upregulation of pro-ADM secretion in patients with prolonged hemodynamic failure and/or with unresolved infection or if it results from its accumulation in patients with renal failure. The measurement of pro-AVP and pro-ADM level is more suitable in the clinical practice because of their longer half-lives. Additionally and unlike vasopressin, pro-AVP has very high in vitro stability and is less bound to platelets in plasma. However, the progressive renal dysfunction often observed in non-survivors of septic shock may increase pro-AVP and pro-ADM levels by affecting their clearance and consequently bias their prognostic significance after several days of evolution. In this sense, a correlation was found between pro-ADM and creatinine levels in a previous study in septic patients [8]. Moreover, continuous veno-venous hemofiltration was also shown to influence the correlation between AVP and pro-AVP plasma levels [11]. Interestingly, the prognostic value of pro-AVP and pro-ADM was not affected by creatinine level in the study of Dr Guignat et al. [10]. However, the implication of renal dysfunction has not been extensively studied.

An interesting issue is the potential use of biomarkers reflecting hemodynamic and cardiac disturbances to guide hemodynamic management of septic shock. Future works should also determine if the production of pro-AVP and pro-ADM is correlated with cardiac insufficiency and with the intensity of the hemodynamic failure during septic shock.

Apart from pro-AVP and pro-ADM, other biomarkers have been shown to have a prognostic significance during sepsis, such as procalcitonin [12] or the natriuretic peptides ANP and BNP and their respective cosynthesized

peptides pro-ANP and pro-BNP [13, 14]. However, only few studies combined different biomarkers to improve their prognostic significance. The study of Dr. Guignat et al. [10] is a good example of this approach. At day 1–2 of septic shock, a pro-AVP level >110 pmol/l associated with a pro-ADM level >5 nmol/l predicted early mortality with a better accuracy than SAPS II or SOFA scores. Among others, the early prognostic assessment is important because the severity of the disease influences the consumption of health-care resources and the indication for intensive care unit admission, both able to influence prognosis. Used in conjunction with clinical assessment, biomarkers may therefore be useful for optimized care of septic patients. However, the additional value of these combinations when compared with scoring systems has to be further evaluated in order to translate their measurement into clinical practice.

In summary, the study of Guignat et al. [10] clearly suggests an increased secretion of both pro-AVP and pro-ADM during septic shock. Like for other promising biomarkers, their production is correlated with prognosis. However, it remains to be evaluated if their production is inadequately upregulated or if it reflects an adaptative response to shock that could be even insufficient. Like cortisol, AVP and ADM partly reflect the level of stress of the organism, and it has been established that a relative cortisol insufficiency is better correlated with prognosis during sepsis than its increase [15]. The study of Guignat et al. [10] is an observational study and does not allow drawing any conclusion concerning therapeutic interventions. However, the observed correlation between the pro-AVP or pro-ADM level and prognosis in septic shock patients highlights the interest in studying AVP and ADM as potential therapeutic targets in future research.

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