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Editorial Comment

RELATIVE ADRENAL INSUFFICIENCY IN CARDIOGENIC SHOCK: IS THERE A NEED FOR ACTION?

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It has been recognized for many years that the functional integrity of the hypothalamic pituitary axis is compromised during severe infection. The observed blunted response to corticotropin was interpreted as impaired secretory reserve of the adrenal glands and was denoted as relative adrenocortical insufficiency (RAI). In septic shock, a blunted response to corticotropin prognosticates poor outcome, but resolves after complete recovery (1, 2). Combined with a decreased cellular sensitivity to steroids, the blunted response to corticotropin was proposed to define critical illness-related corticosteroid insufficiency. The international ACCM/SCCM task force used this term to highlight that any critical illness associated with an overwhelming systemic inflammation may compromise adrenocortical function, though the majority of studies related to RAI focused on patients in septic shock.

The concept of RAI in critical illness is still a matter of debate. In a milestone study published a few years ago, Boonen et al. clearly demonstrated that cortisol clearance is reduced to 40% in critically ill patients with hyperlactatemia (2.58 mmol/L) and 34 points APACHE II score. The lower clearance was deemed responsible for the elevated cortisol levels observed in critical illness (3). Interestingly, the lower cortisol clearance was also associated with less cortisol response to corticotropin (3). Although high cortisol levels appear to argue against a syndrome of corticosteroid insufficiency, the combination of high cortisol levels and a blunted response to corticotropin showed the poorest prognosis in septic shock (1).

Despite these new insights into cortisol metabolism during critical illness, the prognostic value of a short corticotropin test has been demonstrated in many studies, also in shock states not caused by sepsis. In this issue of *Shock*, Bagate et al. (4) demonstrate that a blunted response to corticotropin was an independent predictor for hospital and long-term mortality in patients with cardiogenic shock. By combining cortisol levels at baseline with the increase of cortisol after corticotropin, the authors proposed a prognostic risk classification of three groups. Based on the data of 92 patients with cardiogenic shock, adrenal response to corticotropin was considered to be inappropriate with an increase in cortisol $\leq$473 nmol/L. In presence of high cortisol levels at baseline (>798 nmol/L) this group of patients had the poorest long-term prognosis.

Cardiogenic shock shares immune mechanisms with septic shock. Low-flow state and systemic inflammation causes endothelial damage and organ dysfunctions very similar to sepsis. Inflammatory mediators, oxidative stress, and overproduction of nitric oxide may be responsible for vasodilation and low systemic vascular resistance observed in many patients with confirmed cardiogenic shock complicating acute myocardial infarction. Excessive oxidative stress as present in shock has been identified to suppress steroidogenesis in adrenal glands (5). This may explain why the adrenal responsiveness is altered in the majority of patients with severe cardiogenic shock.

The key question to answer is whether to treat or not to treat RAI in cardiogenic shock. In septic shock, two large-scale randomized trials gave conflicting results: Short corticotropin test identified patients who showed a benefit to steroid treatment in one study, but not in the other study. Studies revealed interassay variations in samples of patients with septic shock thus complicating the diagnosis of RAI (6). Other confounding factors like the use of etomidate, deep sedation, or a preceding long-term treatment with corticosteroids may further complicate the correct diagnosis of RAI in the individual patient. For these reasons, the surviving sepsis campaign does not recommend corticotropin testing in septic shock to indicate steroid treatment.

In a gene knockout model simulating RAI (i.e., a murine model that shows normal corticosterone level under physiologic conditions, but a lack of inducible corticosterone production in response to corticotropin or septic stress) treatment with corticosteroid protected against sepsis after cecal ligation and puncture. This study also showed that steroids may harm wild-type mice with unaltered adrenocortical responsiveness (7). A harm of steroid therapy in human septic shock has not (yet) been demonstrated. However, a small pilot study in patients with cardiogenic shock found that corticosteroids therapy was an independent risk factor of death in a logistic regression model (8).

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So, what shall we do? First, we should not harm patients. In other words, steroid treatment of patients with cardiogenic shock should only be used in controlled clinical trials. Second, we need more information on compromised adrenocortical function in shock states. The use of corticotropin test is a good first step. The goal is to identify patients who should, and—more important—patients who should not be treated with steroids.

REFERENCES

1. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 283(8):1038–1045, 2000.
2. Briegel J, Schelling G, Haller M, Mraz W, Forst H, Peter K: A comparison of the adrenocortical response during septic shock and after complete recovery. *Intensive Care Med* 22(9):894–899, 1996.
3. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden YM, Spriet I, Wouters PJ, Vander Perre S, et al.: Reduced cortisol metabolism during critical illness. *N Engl J Med* 368(16):1477–1488, 2013.
4. Bagate F, Lellouche NLP, Lim P, Moutereau S, Razazi K, Carteaux G, de Prost N, Dubois-Randé JL, Brun-Buisson C, Dessap AM: Prognostic value of relative adrenal insufficiency during cardiogenic shock: a prospective cohort study with long-term follow-up. *Shock* 47(1):86–92, 2016.
5. Prasad R, Kowalczyk JC, Meimaridou E, Storr HL, Metherell LA: Oxidative stress and adrenocortical insufficiency. *J Endocrinol* 221(3):R63–R73, 2014.
6. Briegel J, Sprung CL, Annane D, Singer M, Keh D, Moreno R, Möhnle P, Weiss Y, Avidan A, Brunkhorst FM, et al.: Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. *Intensive Care Med* 35(12):2151–2156, 2009.
7. Ai J, Guo L, Zheng Z, Wang SX, Huang B, Li XA: Corticosteroid therapy benefits septic mice with adrenal insufficiency but harms septic mice without adrenal insufficiency. *Crit Care Med* 43(11):e490–e498, 2015.
8. Tol MM, Shekar K, Barnett AG, McGree J, McWhinney BC, Ziegenfuss M, Ungerer JP, Fraser JF: A preliminary investigation into adrenal responsiveness and outcomes in patients with cardiogenic shock after acute myocardial infarction. *J Crit Care* 29(3):470, 2014.