Paul E. Marik
Alexander Levitov

The “koala stress syndrome” and adrenal responsiveness in the critically ill

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P. E. Marik (✉) · A. Levitov
Division of Pulmonary and Critical Care Medicine,
Eastern Virginia Medical School, 825 Fairfax Av, Suite 410,
Norfolk, VA 23507, USA
e-mail: marikpe@evms.edu

Virtually all stressors, including infections, physical trauma, and even psychological insults, result in activation of the hypothalamic–pituitary–adrenal (HPA) axis with the release of cortisol [1]. At low basal levels cortisol binds to the high affinity, low capacity mineralocorticoid receptor (MR). However, with increased cortisol secretion the MRs are saturated and cortisol then binds to the low affinity, high capacity glucocorticoid receptor (GR). The cortisol–GR complex acts via multiple genomic and non-genomic mechanisms to enhance cardiovascular reserve and provide a ready source of fuel (glucose) for the brain and musculoskeletal system, allowing the organism to take appropriate action (flight or fight) while preventing excessive activation of the immune system [2]. In addition, the increase in serum cortisol during stress protects the organism against developing post-traumatic stress disorder (PTSD) [3]. The fight and flight response is essential for survival and is present in the most primitive of species. Furthermore, within species the degree of activation of the HPA axis has evolved to match the degree of stress to which the organism is exposed (see Fig. 1). The koala (*Phascolarctos cinereus*) is a herbivorous marsupial native to Australia which evolved in an

environment with no natural predators. Consequently the koala has a vestigial adrenal gland and is unable to produce cortisol when challenged (by man) and instead of running away or fighting will go into a state of shock known as the “koala stress syndrome”. As is evident from Fig. 1, humans have evolved in a stressful environment and consequently have a brisk increase in cortisol in response to stress. Hypoxia, hypotension, and sepsis are amongst the most potent activators of the HPA axis and critically ill patients therefore usually have very high cortisol levels. When cortisol synthesis is blocked (with an etomidate infusion) the mortality of critically ill patients increases dramatically [4]. As a result of decreased cortisol secretion and/or tissue resistance (GR abnormalities) inadequate corticosteroid activity is present in many critically ill patients, particularly those with sepsis. This condition has been termed critical illness-related corticosteroid insufficiency (CIRCI) [5, 6]. The presence of CIRCI may increase the morbidity and mortality of critically ill patients and predispose to PTSD [6–9].

The diagnosis of CIRCI is fraught with difficulties and at present this diagnosis is best made by a random (stress) cortisol of less than 10 µg/dl or a delta cortisol of less than 9 µg/dl after a 250 µg ACTH stimulation test [5, 6, 10]. One approach to resolving the question of whether too little glucocorticoid signal ultimately “gets through” is to examine target tissues whose function is regulated in part by glucocorticoids. Through their inhibitory effects on nuclear factor- $\kappa\beta$ signaling pathways, glucocorticoids are the most potent anti-inflammatory hormones in the body and thereby serve to suppress the production and activity of proinflammatory cytokines during exposure to stress. Inadequate glucocorticoid-mediated feedback inhibition of the immune response will result in excess circulating levels of proinflammatory mediators.

In this edition of *Intensive Care Medicine*, Kwon et al. [11] measured the levels of proinflammatory mediators in

Fig. 1 Basal and stressed cortisol level amongst various animal species

a cohort of 82 patients, most of whom had sepsis. Thirty-six patients (43%) met the criteria for CIRCI. The authors divided the patients with CIRCI into two groups, namely (1) those with a low basal cortisol (basal cortisol <10 µg/dl) and (2) those with a basal cortisol of at least 10 µg/dl and a delta cortisol less than 9 µg/dl. In the group of

patients with a low delta cortisol, the serum levels of proinflammatory mediators were markedly elevated compared to the group of patients with a low basal cortisol. In the low basal cortisol group the levels of proinflammatory mediators were similar to those of the non-CIRCI control patients. These data suggest that the CIRCI subgroup with a low delta cortisol may truly have too little glucocorticoid signaling while the low baseline subgroup appears to have adequate cellular glucocorticoid activity. From a pathophysiological and therapeutic standpoint it may therefore be useful to divide CIRCI into two subgroups, namely: type I, characterized by a random (stress) cortisol of less than 10 µg/dl; and type II, characterized by a random cortisol of at least 10 µg/dl and a delta cortisol less than 9 µg/dl. The practical implication of this classification is that only patients with type II CIRCI may benefit from stress doses of corticosteroids. Additional studies are required to confirm the findings of Kwon et al. and future studies investigating the role of treatment with corticosteroids should a priori divide the patients into CIRCI subgroups.

Conflict of interest The authors have no financial interest in any of the products mentioned in this paper.

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