

## EDITORIAL

# New perspectives in interpretation and treatment of hormonal dysregulation in critically ill patients

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All critically ill patients admitted to the intensive care unit (ICU) have a similar adaptive endocrine and metabolic dysregulation in response to major trauma, extensive surgery or severe medical disease. The hormonal stress response to critical illness follows a biphasic pattern.<sup>[1]</sup> The acute phase starts within minutes or hours after the deleterious event with a decrease in anterior pituitary hormones. A number of patients fail to recover sufficiently within a few days and enter a chronic phase of critical illness. In the acute phase, the fight or flight state is activated by the release of cytokines and noradrenaline resulting in a catabolic state in order to provide enough energy to survive. However, patients who survive this acute phase and remain dependent on vital organ support show attenuated central and peripheral hormone levels across all axes.<sup>[1,2]</sup> Replacement therapy seems an obvious next step in order reach an anabolic state in the ICU and thereafter.

The obviously critically ill patient will be resuscitated immediately in order to achieve normal values. Glucose is the main substrate to produce energy with enough oxygen brought into the tissue by sufficient blood flow. However, the hormonal and metabolic dysregulation in the acute phase is not visible at the bedside. Almost all critically ill patients suffer from insulin resistance and are treated with insulin. Additionally, in patients with refractory shock or severe inflammation, the intravenous administration of several catabolic hormones (adrenaline, noradrenaline, dopamine, dobutamine, hydrocortisone, dexamethasone) will be started to achieve a normal blood pressure or attenuate the inflammatory response. During their stay at the ICU several other hormones are currently prescribed, such as nandrolone, somatostatin, vasopressin or medication that indirectly inhibits endogenous cortisol secretion or dysregulates thyroid function.<sup>[1,3]</sup>

Critically ill patients develop hyperglycaemia and insulin resistance resulting in adverse outcomes. In previous studies, intensive insulin therapy (IIT) to achieve normoglycaemia was proven to reduce mortality and morbidity in critically ill patients

post thoracic surgery.<sup>[4]</sup> Since the release of this landmark study in 2001, hyperglycaemia was no longer acceptable. However, insulin infusion is potentially lethal because of the risk of prolonged severe hypoglycaemia. The incidence of a hypoglycaemic event in critically ill patients increased significantly during IIT, especially in septic patients.<sup>[5]</sup> In a pilot study the glucagon response to the first hypoglycaemic event after admission to the ICU in septic patients was significantly lower than in post-surgical critically ill patients without sepsis.<sup>[6]</sup> This blunted glucagon response to hypoglycaemia could probably explain why septic patients sometimes have spontaneous hypoglycaemia at presentation and why the incidence of severe hypoglycaemic events was higher in septic than in post-surgical patients, treated according to the same IIT protocol.<sup>[4-6]</sup>

With this wide range of endocrinological interventions and with an increasing number of chronic critically ill patients in the ICU, there is a need for more attention and knowledge of endocrine dysregulation in the critically ill. And in particular, to investigate the effect of administration of high doses of catabolic hormones, the prolonged use of supra-normal insulin levels and immobilisation on the development of ICU-acquired weakness, time to recovery after discharge, chronic fatigue and post-intensive care syndrome (PICS). Further intervention studies are needed to investigate whether replacement therapy could be helpful to prevent or attenuate this negative effect on physical recovery by interventions during their stay in the ICU. For instance, by investigation of timing of replacement therapy, target levels of several hormonal axes, central or peripheral hormonal replacement, pulsatile or continuous hormonal replacement, replacement of all axes at the same time or in a specific order. Several plasma hormone levels remain low for a few months after discharge from the ICU.<sup>[2]</sup> Follow-up post ICU will be helpful to taper or adjust the endocrine replacement therapy and investigate whether endocrine dysfunction remains in patients with PICS. Follow-up post ICU can also be helpful

to detect late complications, for instance primary adrenal insufficiency in patients after meningococcal sepsis due to adrenal haemorrhage. After discharge from the ICU, many patients complain of tiredness and loss of libido and this is usually attributed to PICS. However, this could be due to an insufficient thyroid, adrenal and/or gonadal axis and probably needs temporary replacement therapy.

In this issue, Bech and co-authors nicely investigated the changes in androgen metabolism in male patients with sepsis who required mechanical ventilation to increase the knowledge of its pathophysiology before considering replacement therapy.<sup>[7]</sup> The results are in accordance with a dysregulated gonadal axis with very low testosterone and markedly elevated oestradiol levels, caused by a combination of reduced gonadotropin secretion, reduced androgen precursor availability and increased aromatisation. The question arises whether recovery will accelerate by increasing plasma testosterone levels in male septic ICU patients with hypogonadotropic hypogonadism in the acute and/or in the chronic phase of their disease.

Several anabolic hormones such as thyroid hormone, growth hormone and testosterone are deficient in critically ill patients admitted to the ICU.<sup>[1]</sup> Replacement therapy is obvious, however not yet applied in the ICU. The author who published the IIT study nicely analysed endocrine dysfunction and course in critically ill patients.<sup>[2]</sup> Sick euthyroid syndrome appears within a few hours after onset of critical illness. The altered conversion of thyroxin (T4) results in extremely low levels of triiodothyronine (T3) and high levels of the inactive reverse T3 (rT3).<sup>[8]</sup> Lack of increase in plasma T3 levels during the chronic phase is associated with a higher mortality.<sup>[9]</sup> High doses of T4, T3 or a combination led to overtreatment with further suppression of thyroid-stimulating hormone and a rise in rT3.<sup>[10]</sup> Supplementation of deficient growth hormone with high-dose growth hormone injections to prolonged critically ill patients unexpectedly doubled the mortality in the intervention cohort.<sup>[11]</sup> Infusion with dopamine, in analogy with increased endogenous dopamine, aggravates suppression of circulating pituitary-dependent hormones thyroid-stimulating hormone, prolactin and luteinising hormone in the acute phase and growth hormone in the chronic phase.<sup>[3,12]</sup>

The administration of anabolic steroids or testosterone in male chronically ill patients suffering from ICU-acquired weakness also seems tempting. Studies on the use of androgens in prolonged critical illness failed to demonstrate any benefit. Exogenous pulsatile hypothalamic hormone administration given together with growth hormone secretagogues and thyrotropin-releasing hormone induced an anabolic response.<sup>[13]</sup> So far, no studies focusing on potential clinical outcome benefits have been performed.

The deleterious effects of the administration of several hormones in critically ill patients have already led to adjustments of several drugs in the ICU. We have become careful about the use of etomidate, steroids and amiodarone. Dopamine is generally considered to be fairly obsolete in (non-)cardiogenic shock. In the sepsis guidelines vasopressin prescription is advised in septic shock.<sup>[14]</sup> Interestingly, vasopressin may be used as a first-line vasopressor in patients with vasoplegic shock after cardiac surgery.<sup>[15]</sup> The question arises if this also leads to a reduction of noradrenaline and steroid administration, reduction in gluconeogenesis and muscle atrophy with a lower incidence of ICU-acquired weakness. In daily practice on the ICU, analysis of endocrine dysregulation is limited to the adrenal axis (a synacthen test in order to detect primary adrenal insufficiency) and thyroid axis (in patients with refractory tachycardia using amiodarone).

Until now, many questions remain unanswered. The pathological endocrine response in critically ill patients and the relevance of replacement needs more exploration. The study in this issue by Bech et al. further contributes to unravelling the endocrine response in critically ill septic patients. Treatment of altered hormone levels in the acute phase of critical illness might not be indicated. Treatment with exogenous hormones in the chronic phase of critical illness seems obvious, however experimental studies in the past have shown difficulties and sometimes causing more harm than good. A new area will be treatment with hypothalamic releasing factors instead of peripheral hormones.<sup>[1]</sup>

Finally, I would like to complete this editorial with a compliment to my Dutch colleagues for their contribution in analysing the changes in androgen metabolism in critically ill septic patients. In this sense, I would like to underline the importance to screen the endocrine axes in post-ICU patients with prolonged tiredness and who are only slowly recovering from the ICU. This will help us to identify patients with a maladaptive hormonal course and the potential need for replacement therapy to ultimately increase quality of life in the recovery period.

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