

MECHANISMS IN ENDOCRINOLOGY

New concepts to further unravel adrenal insufficiency during critical illness

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Abstract

The concept of 'relative' adrenal insufficiency during critical illness remains a highly debated disease entity. Several studies have addressed how to diagnose or treat this condition but have often yielded conflicting results, which further fuelled the controversy. The main reason for the controversy is the fact that the pathophysiology is not completely understood. Recently, new insights in the pathophysiology of the hypothalamic–pituitary–adrenal axis response to critical illness were generated. It was revealed that high circulating levels of cortisol during critical illness are explained more by reduced cortisol breakdown than by elevated cortisol production. Cortisol production rate during critical illness is less than doubled during the day but lower than in healthy subjects during the night. High plasma cortisol concentrations due to reduced breakdown in turn reduce plasma ACTH concentrations via feedback inhibition, which with time may lead to an understimulation and hereby a dysfunction of the adrenal cortex. This could explain the high incidence of adrenal insufficiency in the prolonged phase of critical illness. These novel insights have created a new framework for the diagnosis and treatment of adrenal failure during critical illness that has redirected future research.

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Introduction

Adrenal insufficiency acquired during critical illness was first described in 1946 by Hans Selye. Since then numerous studies aimed at further understanding this complex disease. Later, the distinction was made between 'absolute' and 'relative' adrenal insufficiency in the critically ill (1, 2, 3). Absolute adrenal insufficiency as also diagnosed outside the intensive care unit (ICU) by endocrinologists is well characterised and understood and refers to a failing

cortisol production. In contrast, relative adrenal insufficiency (RAI), a term that refers to a functional and likely transient deficiency acquired during critical illness and that implies an insufficiently activated adrenal cortex relative to the degree of stress, is a concept that is the subject of great controversy (4, 5, 6). It is generally accepted that a pronounced and sustained activation of the hypothalamic–pituitary–adrenal (HPA) axis in

Invited Author's profile

Eva Boonen graduated in medicine in 2010 and is currently pursuing post doctoral research at the Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium. During her anesthesiology residency she started a doctoral thesis investigating HPA-axis alterations during critical illness, where she focused predominantly on cortisol metabolism. Her research revealed that cortisol metabolism is markedly reduced during critical illness and reshaped the current view on HPA-axis alterations with further implications for diagnosis and treatment of adrenal insufficiency. As a post-doc researcher her main focus remains HPA-axis alterations during critical illness.



response to critical illness is vital. This is based largely on results of animal experiments revealing that adrenalectomy increases mortality of sepsis (7). However, the underlying mechanisms of RAI during critical illness are incompletely understood, contributing to the ongoing controversy as to whether such a state exists.

The concept of adrenal insufficiency in critical illness

Absolute adrenal insufficiency in critical illness

During critical illness, as well as outside the context of the ICU, absolute adrenal insufficiency has many possible causes (1, 2, 3). Absolute adrenal insufficiency can be divided into primary, secondary and tertiary adrenal failure. Primary adrenal insufficiency is caused by diseases of the adrenal cortex. Adrenal dysfunction due to impaired adrenocorticotrophic hormone (ACTH) secretion because of pituitary abnormalities is labelled secondary adrenal insufficiency, while insufficient arginine-vasopressine or corticotrophin-releasing hormone (CRH) secretion and function can cause tertiary adrenal insufficiency. The most common cause of tertiary adrenal insufficiency is long-term, high-dose glucocorticoid therapy, which suppresses the HPA axis by negative feedback inhibition (1, 2, 3).

During critical illness, patients with a prior history of adrenal insufficiency are at the risk of developing an Addisonian crisis triggered by the stress of the disease. Besides the risk due to pre-existing adrenal insufficiency, new onset absolute adrenal failure can be evoked by critical illness itself. For example, adrenal insufficiency can be due to adrenal hemorrhage or adrenal vein thrombosis, for which ICU patients may be at higher risk given the coagulation disorders present in many types of severe illnesses. In addition, several medications frequently used in ICU can affect cortisol production. Etomidate is one of these drugs and is known to suppress cortisol production, even after a single dose. Other drugs known to influence the HPA axis are azoles, anticoagulants, phenobarbital, phenytoin, rifampin, opioids, chlorpromazine and imipramine (8).

Absolute adrenal insufficiency should be suspected whenever otherwise unexplained hypovolemia and/or catecholamine-resistant hypotension is present, especially when this occurs in a patient who also has hyperpigmentation, hyponatremia or hyperkalemia. A low plasma cortisol concentration with or without a low plasma ACTH concentration and a suppressed cortisol response to an ACTH stimulation test are further indicative of such a diagnosis of absolute adrenal insufficiency.

It is generally accepted that patients with an established diagnosis of primary or secondary adrenal failure or patients on chronic treatment with systemic glucocorticoids prior to critical illness should receive additional coverage with hydrocortisone to cope with the acute stress of the disease (9, 10). Also, patients who are diagnosed with an acute Addisonian crisis in the ICU are typically treated with high doses of glucocorticoids. This therapeutic strategy is based on the assumption that cortisol production during critical illness is several-fold increased as compared with during health. The conventional treatment proposes the administration of an i.v. bolus of 100 mg of hydrocortisone followed by 50–100 mg every 6 h on the first day, 50 mg every 6 h on the second day and 25 mg every 6 h on the third day, tapering to a maintenance dose by the fourth to fifth day (9, 10).

RAI in critical illness

When the degree of HPA-axis activation is assumed to be not enough to cover the need of cortisol to survive, even when plasma cortisol levels are still higher than during health, the condition has been labelled 'RAI' (4). More recently, the term 'critical illness-related corticosteroid insufficiency' (CIRCI) (5, 6) has been introduced, as such 'relative failure' during critical illness can occur at any level of the HPA axis and/or may be due to resistance to cortisol in the peripheral target tissues (5, 6). However, the possible underlying mechanisms remain highly debated. Pro-inflammatory cytokines have been suggested to induce target tissue resistance and to inhibit ACTH function (2, 11, 12). Furthermore, impaired blood supply to the anterior pituitary gland can evoke ischemia or necrosis, accumulation of nitric oxide or central neuropeptides, and hereby decreased ACTH secretion (3). Additionally, several neuropeptides, oxidative stress, altered adrenal blood flow, cortisol precursor deficiency due to low circulating cholesterol levels or medications that suppress cortisol synthesis have also been suggested to play a role (8). Since cholesterol is produced in the liver, patients with liver diseases may have defective cholesterol production, which could increase the risk of adrenal insufficiency. Furthermore, the incidence of coagulopathy is higher in liver disease patients leading a higher risk of adrenal haemorrhage (13). Target tissue resistance to cortisol, the second part of the definition of CIRCI, refers to decreased glucocorticoid cellular uptake or suppressed expression or activation of the glucocorticoid receptor (GR). Low corticosteroid binding globulin (CBG) levels and decreased CBG affinity may impair cortisol transport.

Furthermore, GR expression levels and affinity of the GR for cortisol can be altered by critical illness.

As for absolute adrenal insufficiency, initial diagnosis of suspected RAI starts with the clinical presentation. Hypotension refractory to fluid resuscitation and vasopressors may be signs of CIRCI, even when other symptoms of adrenal failure are absent. Suggested diagnostic criteria for CIRCI in critically ill patients have been based on one landmark study by Annane *et al.* (4) who identified a plasma cortisol incremental response $<9 \mu\text{g/dl}$ (for conversion of cortisol to SI units (nmol/l) multiply by 27.6) after the injection of $250 \mu\text{g}$ ACTH (for conversion of ACTH to SI units (pmol/l) multiply by 0.22) in the face of a high baseline plasma cortisol concentration ($>34 \mu\text{g/dl}$) as most discriminative for an increased risk of death. However, these findings have not been replicated by other investigators, which explains why there is currently no consensus on the diagnostic criteria for RAI (5). Furthermore, also the dose of ACTH that should be used for the ACTH stimulation test remains controversial. A dose of $250 \mu\text{g}$ of ACTH leads to supra-physiologic ACTH levels and could therefore overcome any ACTH resistance. Alternatively, a $1 \mu\text{g}$ stimulation dose has been suggested but the diagnostic value hereof has not been extensively investigated in critically ill patients and the results of the studies have been conflicting (14, 15).

Other authors have suggested that the diagnosis of CIRCI can be made by a random total plasma cortisol concentration $<10 \mu\text{g/dl}$ during critical illness (5). However, total plasma cortisol concentration is derived from the result of adrenal production, secretion, distribution, binding and elimination of cortisol. Also, cortisol is secreted in a pulsatile manner (16). Overall, it thus seems impossible to assess the adrenal cortisol secretion rate with a single random cortisol measurement. Furthermore, total plasma cortisol concentrations give little information about glucocorticoid function. Only free cortisol can cross the cell membrane to exert its function by binding to the GR and consequently binding as a complex in the nucleus. The acute response to critical illness comprises an immediate fall in the circulating levels of the binding proteins, CBG and albumin, together with an altered CBG-binding affinity, which occurs via the cleavage of CBG at the sites of inflammation or in the circulation evoked by fever (17, 18, 19, 20, 21). Plasma free cortisol has been suggested by other authors to be more appropriate than total plasma cortisol for the assessment of the HPA-axis functioning (22, 23). However, plasma free cortisol assays are currently not readily available and normal ranges of plasma free cortisol during critical illness have not been

defined. Additionally, increasing evidence from both animal and human experiments suggests that GR availability in different tissues, the GR affinity and translocation are regulated during critical illness (24, 25, 26, 27, 28, 29). In septic patients, for example, the dominant negative β -isoform of the GR was induced from the onset of critical illness on, which downregulates glucocorticoid action (25). Given the impact of these changes on glucocorticoid function, they limit conclusions about 'adequacy' of cortisol availability during illness. Finally, a lack of accuracy and a high inter-assay variation in cortisol assays (30), further limits the use of one cut-off value of cortisol in clinical practice to define CIRCI. It may be necessary to use mass spectrometry since this method is more accurate and less sensitive to confounders (31, 32).

The most recent guidelines for the treatment of sepsis no longer recommend to use the ACTH stimulation test for the diagnosis of CIRCI (33). Instead, the guidelines suggest to use a random cortisol level $<18 \mu\text{g/dl}$ in a patient with septic shock and clinical suspicion of adrenal failure as an indication for initiation of steroid therapy (33). These current recommendations are still largely based on expert opinion.

Other experts have recently suggested to measure interstitial cortisol levels in critically ill patients to assess the amount of cortisol availability for target tissues (34, 35). To this end, a microdialysis catheter is inserted into the subcutaneous adipose tissue. However, edema is frequently present in the critically ill, regional blood flow is variable and it is unclear what the subcutaneous adipose tissue tells the clinician about the other target tissues of interest in the critically ill (36). The usefulness of this invasive technique thus remains unclear.

Perhaps even more controversial than the diagnostic criteria is the issue of when treatment of CIRCI with exogenous glucocorticoids is required and which doses should be used. This controversy is mainly fuelled by the conflicting results of two large randomised controlled trials (RCT). The first large trial by Annane *et al.* (37) investigated 300 patients with septic shock on vasopressor therapy. All patients received an ACTH stimulation test and were randomly assigned to be treated with placebo or with 200 mg hydrocortisone plus $50 \mu\text{g}$ fludrocortisone/day for 7 days. The study showed that glucocorticoid treatment reduced the duration of vasopressor therapy. There was no overall benefit on survival, but in the subgroup of patients who showed a low cortisol incremental response to the ACTH stimulation test, the treatment reduced 28 days mortality by an absolute 10%. However, the relevance of this subgroup analysis has been

questioned as well as the bias induced by widespread use of etomidate during this study. The repeat RCT also could not confirm this beneficial effect on survival of a treatment with hydrocortisone for septic shock. Indeed, this multicenter randomised-controlled double-blind trial included 499 patients and investigated the impact on 28 days mortality of 200 mg hydrocortisone daily or placebo for 5 days after which a tapering period followed (38). This study revealed that hydrocortisone treatment increased blood pressure but did not improve survival, neither in the non-responders to ACTH stimulation, nor in the entire population. Moreover, an increased incidence of septic shock relapse was observed. However this study was also criticised, mainly for its early stop due to slow patient recruitment, which reduced the statistical power of the trial.

A systematic review of all high-quality RCTs recently concluded that hydrocortisone therapy does not reduce mortality of severe sepsis (39). Recent guidelines now recommend, although with a weak level of confidence, to only treat patients with hypotension refractory to vasopressor or fluid resuscitation. A dose of 200 mg hydrocortisone via continuous infusion is advised, with a quick tapering down of the dose whenever vasopressors are no longer needed. The guidelines do not advise glucocorticoid treatment for patients with sepsis without shock (33).

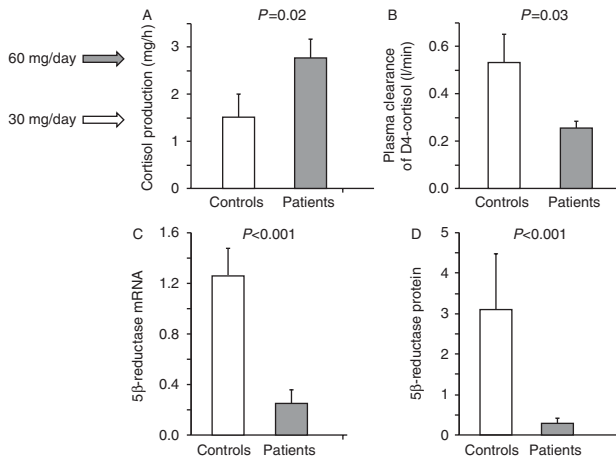
Better understanding the HPA-axis regulation during critical illness?

Further optimization of diagnosis and treatment of critical illness-induced adrenal insufficiency clearly requires a better understanding of the HPA-axis pathophysiology in this context. The stress response is considered to start at the level of the hypothalamus, with the release of CRH into the portal circulation, which stimulates the pituitary corticotrophs to secrete ACTH, in turn activating the production and release of cortisol in the adrenal cortex. Negative feedback inhibition by cortisol at the level of CRH and ACTH can turn off this activation of the HPA-axis to regain homeostasis. Critical illness is considered to be a condition of severe physical stress and the typically high plasma free and total cortisol concentrations are assumed to be explained by such a stress-induced HPA-axis activation with several-fold increased cortisol production. However, an observation which does not support such an HPA-axis activation during critical illness is the low plasma ACTH. Vermes *et al.* (40) showed that plasma ACTH concentrations in patients suffering from severe trauma or sepsis were only transiently elevated and after a few days dropped

below those observed in healthy control subjects in the face of high plasma cortisol. Furthermore, in a more heterogeneous long-stay ICU patient population, plasma ACTH concentrations were found to be suppressed from day 1 in ICU throughout the first week of critical illness, again in the presence of high plasma cortisol (41).

This dissociation between ACTH and cortisol suggested that non-ACTH-mediated mechanisms regulate cortisol availability during critical illness. Theoretically, an increased sensitivity for ACTH might explain low ACTH and concomitantly high cortisol. However, since the incremental cortisol response to an ACTH stimulation test during critical illness is never increased and often low, this appears unlikely (4). The possible role of other non-ACTH stimulators of cortisol production in the adrenal cortex has often been suggested (12). Animal and cell culture studies investigated the role of cytokines, neuropeptides and other mediators of such an increased cortisol production. However, since cortisol production had not been quantified in the context of modern intensive care until recently, the long-standing assumption of a several-fold increased cortisol production during critical illness was based only on extrapolation from the increased circulating (free) cortisol levels. Recently cortisol production was quantified during critical illness with the use of the gold standard deuterated cortisol tracer technique (41). This study showed that daytime cortisol production during critical illness was only twice that of healthy subjects, but found that cortisol breakdown was substantially reduced which resulted in a fivefold longer half-life of cortisol, which explained the high plasma cortisol levels (Fig. 1). The reduced cortisol breakdown was explained by suppressed expression and activity of A-ring reductases in the liver and by suppressed activity 11 β -hydroxysteroid dehydrogenase type 2 in kidney (41). A subsequent study that used deconvolution analysis, taking the fivefold longer cortisol half-life into account, showed that nocturnal cortisol secretion was actually lower than in healthy subjects (42). Hence, the 24-h cortisol production rate in many critically ill patients with high plasma cortisol levels may not be much higher compared with the healthy controls.

In this concept, the low plasma ACTH concentrations may well be explained by negative feedback inhibition exerted by elevated plasma cortisol brought about by reduced cortisol breakdown. If ACTH levels remain suppressed for an extended period of time, this could have adverse consequences for the integrity of the adrenal cortex, which would be relevant predominantly in the prolonged phase of illness. A study of adrenal cortex

**Figure 1**

(A) represents cortisol production in critically ill patients ($n=11$, grey bar) compared with the controls ($n=9$, white bar). (B) represents cortisol plasma clearance after a small dose of deuterated-cortisol tracer. Bar charts represent means and standard errors. Based on these results, 24-h cortisol production was estimated and depicted with the arrows. (C) and (D) show mRNA and protein expression of 5 β -reductase in liver of 20 controls (white bar) and 44 patients (grey bar). Bar charts represent means and standard errors. The mRNA data are expressed, normalised to GAPDH, as a fold difference from the mean of the controls. Protein data are expressed normalised for CK-18 protein expression, as a fold difference from the mean of the controls. Figure reproduced from Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden YM, Spriet I, Wouters PJ & Vander Perre S. Reduced cortisol metabolism during critical illness. *New England Journal of Medicine* 2013 **18** 1477–1488. Copyright © (2013) Massachusetts Medical Society. Reprinted with permission.

biopsies harvested post-mortem from acute and prolonged (7 days or more) critically ill patients and from sudden out of hospital deaths showed a very pronounced depletion of cholesterol esters and suppressed expression of ACTH-regulated genes in adrenal glands from prolonged, but not acute, critically ill patients (43). Unfortunately, given the nature of the study, blood samples were not available to correlate the observed changes with plasma ACTH and cortisol concentrations. However, these results are strikingly reminiscent of the phenotype of pro-opiomelanocortin-deficient mice, which suggests that a sustained lack of ACTH-effect on the adrenal cortex may indeed explain these findings (44). These changes in the adrenal cortex of prolonged ICU stay-patients also help to explain the reported 20-fold higher incidence of

symptomatic adrenal insufficiency in critically ill patients being treated in the ICU for more than 14 days (45).

A new context in which to reconsider diagnosis and treatment of adrenal insufficiency during critical illness?

The recent novel insights have reshaped the understanding of the HPA-axis regulation during critical illness, but have also provided a new context in which to reconsider diagnosis and treatment of adrenal insufficiency in that setting.

First, if a primary adrenal failure would be the reason for an insufficiently increased cortisol production and thus insufficiently increased plasma cortisol concentrations, one would expect a high plasma ACTH concentration, which has not been reported (40, 41). Secondly, it was shown that the cortisol incremental cortisol response to an ACTH stimulation test in critically ill patients correlated positively with both cortisol production rate and cortisol plasma clearance (41) (Fig. 2). Patients who revealed a low cortisol response to ACTH, below the threshold of absolute adrenal failure (46) were the ones who also had the most reduced cortisol breakdown, whereas their cortisol production rate was still comparable with that of the healthy subjects. This small piece of evidence could suggest that a low incremental cortisol response to an ACTH injection give little information about the adequacy of cortisol production but may reflect the degree of reduced cortisol metabolism leading to increased cortisol levels that exert a certain degree of negative feedback. This would be comparable with what is observed in patients and who are treated with exogenous glucocorticoids for an extended time, as they also reveal a suppressed cortisol response to ACTH injection, in the face of very high levels of (exogenous) glucocorticoids (47). Thirdly, the response to an ACTH stimulation test is poorly reproducible in critically ill patients (48) and increasing evidence supports the hypothesis that adrenal function during critical illness is dynamic. Therefore, perhaps the use of repetitive measurements of plasma cortisol over time together with repetitive ACTH stimulation tests could shed more light on the nature of adrenocortical dysfunction in critically ill patients. It has already been suggested that the cortisol responsiveness to ACTH restores after recovery of illness, while a decreasing cortisol response during repetitive ACTH-testing was associated with a poor prognosis (23, 49, 50). Unfortunately, large enough and well-designed prospective clinical studies of systematic ACTH stimulation tests

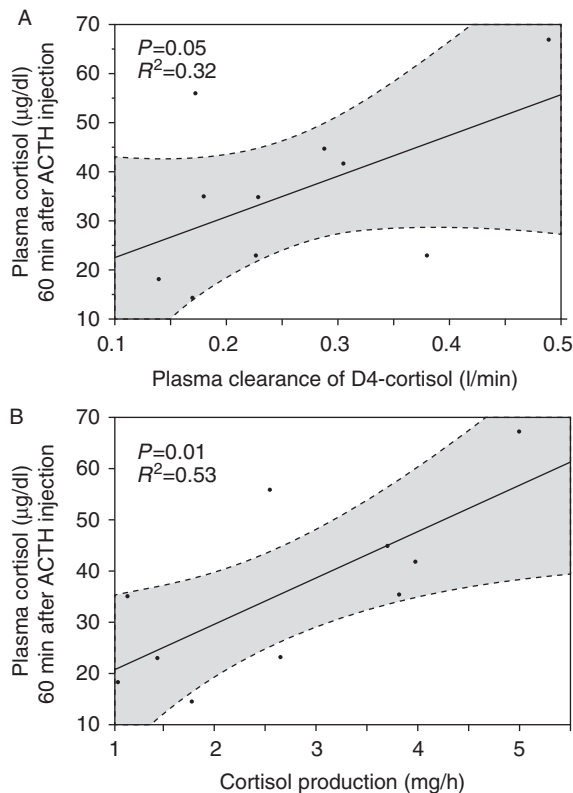


Figure 2

(A) shows the correlation between plasma clearance of D4-cortisol with plasma cortisol responses, 60 min after ACTH injection (250 µg) among patients ($n=10$). (B) shows the correlation between cortisol production with plasma cortisol responses, 60 min after ACTH injection (250 µg) among patients ($n=10$). The shaded area represents 95% CI. Figure reproduced from Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden Y-M, Spriet I, Wouters PJ & Vander Perre S *et al.* Reduced cortisol metabolism during critical illness. *New England Journal of Medicine* 2013 **18** 1477–1488. (doi:10.1056/NEJMoa1214969) Copyright © (2013) Massachusetts Medical Society. Reprinted with permission.

performed on repeated time points into the prolonged phase of critical illness and recovery are currently lacking.

The use of repetitive cortisol measurements may be additionally important, taking into account the limitations of a single total or free cortisol measurement. If persistently low circulating ACTH levels lead to the downregulation of ACTH signalling in the adrenal cortex (43), this could compromise adrenal function and preclude any additional cortisol to be produced whenever a next problem occurs during prolonged critical illness. This would be reflected in a progressively lower plasma

cortisol concentrations with time, coinciding with a lowering of the incremental cortisol response to an ACTH test. Such a time course was already suggested by a recent small study that showed that plasma cortisol levels decreased in the prolonged phase of illness (51).

Also the time course of repetitive quantification of plasma ACTH, concomitantly measured with repetitive plasma cortisol and integrated with the results of repetitive ACTH tests, could be quite informative. Indeed, if sustained negative feedback inhibition by high cortisol that is not broken down play a role in the suppression of plasma ACTH during sustained critical illness, one could expect that plasma ACTH levels rise as soon as cortisol breakdown increases again with recovery. On the other hand when the ACTH levels remain low, the coinciding effect on the adrenal cortex would limit sufficient cortisol availability in the prolonged critically ill due to decreased cortisol production and may indicate who would benefit from treatment with hydrocortisone (Fig. 3).

Recent insights indeed stress the importance of correctly identifying patients with a truly failing adrenal cortex for treatment. A recent animal study showed that corticosteroid treatment is only beneficial in septic mice with an absolute adrenal insufficiency, while it harmed the mice without such adrenal insufficiency (52). Besides the importance of accurately determining ‘who’ to treat, it also should be further investigated ‘how’ to best treat these patients. The currently proposed dose of 200 mg of hydrocortisone/day, referred to as ‘low dose’ in the literature, is in fact between three- and sixfold higher than the cortisol production rate that was recently quantified in critically ill patients (41). Furthermore, given the fivefold longer cortisol half-life in critically ill patients than in healthy control subjects, the hydrocortisone doses of 200 mg/day will expectedly result in high circulating (and possibly also tissue) cortisol levels during critical illness, with risks of side effects (41). Reducing cortisol breakdown may also be a clever mechanism during illness to regulate cortisol availability in a tissue-specific manner, directing high availability to those organs that express the cortisol metabolizing enzymes such as liver and kidney, while this could prevent too high levels of cortisol in those tissues that are susceptible to excessive glucocorticoid exposure such as skeletal muscle. Treatment with exogenous glucocorticoids in too high doses expectedly will increase cortisol availability in all tissues explaining the potentially deleterious effects of this treatment (53, 54). In fact, the novel finding of an increased cortisol half-life during critical illness not only affects the decision on who and how to treat for adrenal failure, but should also be

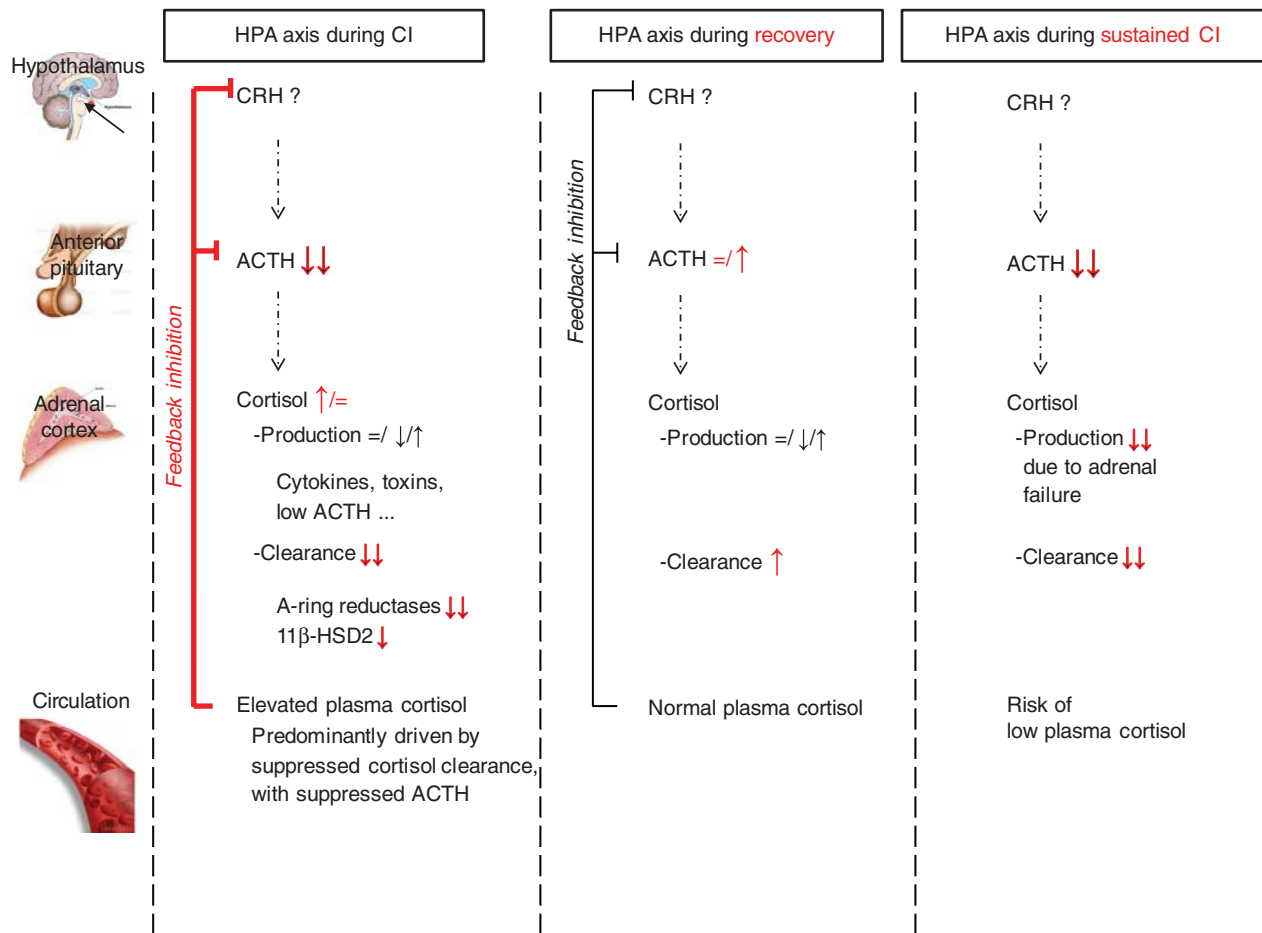


Figure 3

Schematic overview of the HPA-axis regulation during critical illness, recovery or sustained critical illness.

taken into account for treatment of ICU-patients with steroids for other indications. It is clear that more research is urgently needed to clarify the diagnostic and therapeutic implications of the novel pathophysiological insights.

Can preliminary recommendations be made?

While we eagerly await well-designed clinical studies to provide more evidence on how to better diagnose and treat critically ill patients with adrenal failure, perhaps some empirical recommendations can be made. During the acute phase of illness, there is little or no evidence to support the presence of 'relative adrenal failure' requiring treatment. Long-stay patients with symptoms consistent with adrenal failure and decreasing random plasma cortisol together with a progressively lowering of the cortisol response to repetitive ACTH stimulation tests could be at risk of suffering from critical illness-induced adrenal failure.

The experimental guideline applied at the authors' institution identifies patients at risk of having adrenal failure eligible for treatment by the following rule of thumb: critically ill patients with symptoms (unexplained vasoplegia and/or coma for example) who are in the ICU for more than 6 days, with progressively decreasing plasma baseline cortisol concentrations that fall below 6 µg/dl and with an incremental cortisol response to an ACTH stimulation test (250 µg i.v. bolus) of <6 µg/dl. Evidently, these specific threshold levels only apply to the institution's assay (RIA from Immunotech, Prague, Czech Republic) and cannot be extrapolated to other assays without comparative validation studies.

Regarding treatment, historical doses of 200 mg hydrocortisone/day are likely too high given the substantially increased cortisol half-life during critical illness. Based on the stable isotope studies (39) it appears that a dose of ~ 60 mg of hydrocortisone, as extrapolated from

the tracer study, may be interesting to investigate in future studies. A tapering down to the lowest effective dose as soon as possible should be advised to limit any adverse effects of excessive amounts of glucocorticoids during critical illness.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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