

ADRENAL AXIS IN CRITICAL ILLNESS

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Abstract After a stressful event, adaptative mechanisms are carried out to support vital functions. Hypothalamic-pituitary-adrenal axis plays a key role in stress response regulating metabolism, cardiovascular function and immune system. This review addresses pathophysiological changes of the adrenal axis during critical illness, recognizing limitations of methods applied for its evaluation in this special context and defining indications for corticosteroid replacement in critically ill patients. The concept of relative adrenal insufficiency should be abandoned; cosyntropin stimulation test should not be performed for diagnosis of adrenal insufficiency in critical illness nor for establishing the need of treatment.

Key words: cortisol, metabolism, adrenal insufficiency, critical illness

Resumen *Eje adrenal en la enfermedad crítica.* Diversos mecanismos adaptativos se ponen en marcha para sostener las funciones orgánicas vitales en el paciente crítico. El eje hipotálamo-hipófiso-adrenal tiene un papel clave en la respuesta al estrés al regular el metabolismo, la función cardiovascular y la respuesta inmune. Esta revisión tiene por objetivos analizar los cambios fisiopatológicos que se producen en el eje adrenal durante la enfermedad crítica, reconocer las limitaciones de los métodos diagnósticos y definir indicaciones de tratamiento de reemplazo corticoideo en este contexto. El concepto de insuficiencia adrenal relativa debe ser descartado y no se recomienda el test de estímulo con cosintropina para diagnóstico de insuficiencia adrenal durante enfermedad crítica ni para definir la necesidad de tratamiento.

Palabras clave: cortisol, metabolismo, insuficiencia adrenal, enfermedad crítica

KEY POINTS

- Diagnosis of adrenal insufficiency during critical illness should consider the past medical history, current medications, the pathophysiological changes in hypothalamic-pituitary-adrenal axis (decreased cortisol catabolism, reduced binding proteins, increased distribution volume, differential glucocorticoid receptor expression, etc.) and the limitations of diagnostic methods in this context.
- Diagnosis relies on serum total cortisol levels according to binding protein levels. Cosyntropin stimulation test should be avoided in critically ill patients.
- Treatment with hydrocortisone, if needed due to adrenal insufficiency, should not exceed 200 mg daily and be tapered as soon as possible to the physiological dose.

Stress is an unexpected event that alters homeostasis. When caused by severe illness or traumatism, surgery or extended burns, stress threatens life¹. Many times,

management in intensive care unit is mandatory, due to severe respiratory, cardiovascular and/or neurological derangement, conditioning the individual to be defined as a critically ill patient.

In this scenario, several adaptative mechanisms are carried out to support vital functions and to recover homeostasis. Main objectives are assuring perfusion and energy availability for crucial tissues through maintenance of blood pressure and stimulus of gluconeogenesis and glycogenolysis, respectively¹⁻³.

Adaptative mechanisms such as sympathetic and hypothalamic-pituitary-adrenal axis (HPAA) activation exert immediate effects. While somatotroph activation and glucagon secretion occur in a deferred manner^{1,4}.

Cortisol plays a key role in stress response: it contributes to energy supply by increasing catabolism and delaying anabolism. Additionally, it regulates immune system, cardiovascular function and hydroelectrolytic balance¹.

This review addresses pathophysiological changes of HPAA during critical illness, recognizing limitations of methods applied for HPAA evaluation in this special context and defining indications for corticosteroid replacement in critically ill patients.

Received: 25-VI-2020

Accepted: 13-X-2020

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Hypothalamic-pituitary-adrenal axis regulation in critical illness

Activation of hypothalamic-pituitary-adrenal axis (HPAA) in response to critical illness is an immediate event after injury. Hypothalamic corticotropin releasing hormone (CRH) stimulates adrenocorticotrophic hormone (ACTH) secretion from the pituitary. The later induces cortisol production in adrenal glands and as long as cortisol cannot be stored in the adrenals, its availability relays on synthesis in response to stress⁵.

Subsequently, although cortisol production declines, serum free cortisol levels increase⁶⁻⁸, because levels and affinity of cortisol binding globulin (CBG) decrease⁹⁻¹¹. Thus, cortisol bioavailability raises and triggers hypothalamic-pituitary feedback, leading to diminished CRH and ACTH levels and pulsatility 24 hours after injury^{6, 12}.

Concurrently, in this second phase, level and activity of hepatic and renal metabolizing enzymes decrease, driving the prolongation of cortisol half-life^{6, 13, 14}. This explains how

serum free cortisol levels remain elevated (5 to 7 times normal), despite reduction in cortisol production^{6,12, 15-17}.

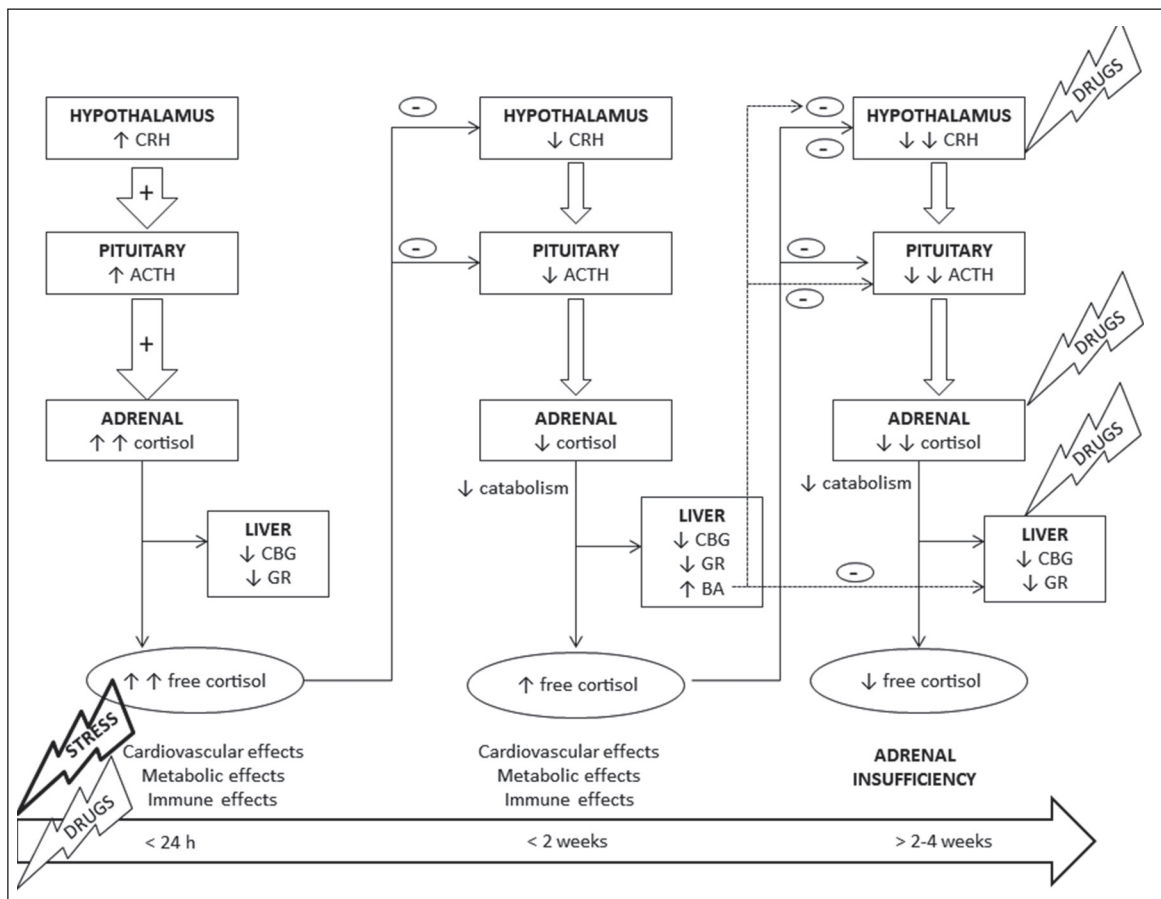
Decreased cortisol catabolism becomes an energetically inexpensive mechanism of maintaining adequate levels of cortisol. Limitation of anabolic processes is crucial while low energy availability exists. However, prolonged low ACTH levels causes structural and functional adrenocortical impairment¹⁸, culminating in adrenal insufficiency after 2 to 4 weeks (Fig. 1)^{1, 18-20}.

Another hypothesis concerning adrenal ACTH-independent stimulation during stress, argues involvement of adrenergic, immune mediators (interleukins 1 and 6, tumor necrosis factor), adipokines and endothelial neuropeptides^{21, 22}.

Cortisol rhythm in critically ill patients lacks of the physiological evening reduction, the normal suppression after dexamethasone administration and shows exaggerated response to CRH, characteristics that assimilate it to Cushing's syndrome²³⁻²⁵.

Finally, the need of increased cortisol production during critical illness for survival is uncertain²⁶. In fact, there

Fig.1.– Hypothalamus-pituitary-adrenal axis regulation in critical illness (adapted from⁶)



CRH: corticotropin releasing hormone, ACTH: adrenocorticotrophic hormone, CBG: cortisol binding globulin, GR: glucocorticoid receptors, BA: bile acids

is no cortisol threshold below which mortality has been augmented²¹.

Variables to consider in critical illness

Cortisol kinetics in the bloodstream

In basal conditions, considering a total cortisol of 15 mcg/dl, 90% of cortisol binds to carrier globulins (75% to CBG -11 mcg/dl- and 15% to albumin -2.5 mcg/dl-). The remaining 10% corresponds to serum free cortisol (1.5 mcg/dl) that is readily available for biologic actions⁶.

In critically ill patients, these proportions differ due to decreased CBG and albumin levels. Considering total cortisol of 15 mcg/dl, cortisol binding to CBG represents approximately 58% (8.6 mcg/dl) and to albumin 11% (1.7 mcg/dl), whereas serum free cortisol raises to 31% (4.7 mcg/dl)²³.

Cortisol changes exhibit variability among individuals depending on sex, heterogeneity and duration of sub-jacent critical illness, hydration state, protein levels, polymorphism of glucocorticoid receptors, CRH and ACTH levels and activity of metabolizing enzymes, in addition to methodological variability of cortisol measurement²¹.

It is important to recall that hepatic inflammation induces protein synthesis, including CBG that can raise serum total cortisol as opposed to critical illness. As a consequence, cortisol levels increase even in this last scenario²⁷.

Due to the impossibility of CBG measurement in clinical practice, albumin is a useful subrogate marker for protein levels. Albumin levels lower than 2.5 g/dl indicate a hypoproteinemic state. Cortisol cut-off is defined

accordingly for adrenal insufficiency definition in critical illness: for albumin level ≥ 2.5 g/dl, adrenal sufficiency is considered when serum cortisol is > 15 mcg/dl and insufficiency if cortisol is < 10 mcg/dl. Whereas if albumin level is < 2.5 g/dl, adrenal sufficiency is considered with cortisol level > 11 mcg/dl and insufficiency when cortisol is < 8 mcg/dl^{17,28} (Fig. 2).

Furthermore, there is still no consensus regarding levels of serum free cortisol considered normal in critical illness. Levels of cortisol during major stress are supposed to be similar to those reached during cosyntropin stimulation test. Therefore serum free cortisol levels in critically ill patients are proposed to be >1.8 mcg/dl²³.

Cortisol metabolism

There are different pathways to metabolize cortisol in renal and hepatic tissues. The renal pathway is mediated by the 11 β -hydroxysteroid deshydrogenase type 2, which converts cortisol to the inactive form cortisone. Activity of this enzyme is decreased in critical illness (approximately by 50%), diminishing cortisol catabolism¹⁴.

In the liver, different enzymatic subgroups with 5-reductase activities (α y β) convert cortisol to inactive metabolites through tetrahydroxylation (5 α - y 5 β -tetrahydrocortisol). These enzymes have reduced activity in critically ill patients, contributing to decreased cortisol breakdown^{12,29}.

Globally, cortisol catabolism in critical illness is estimated to be 47% lesser than in healthy individuals. Moreover, reduced enzyme activity is not the only mechanism to decrease cortisol metabolism but also reduced enzyme synthesis, demonstrated by low mRNA and protein levels¹².

Fig. 2.– Cortisol cut-off for adrenal insufficiency diagnosis according to protein levels (adapted from^{21, 23})

Normoproteinemia (albumin ≥ 2.5 g/dl):		
Cortisol < 10 mcg/dl POSSIBLE AI	Cortisol 10-15 mcg/dl CONSIDER AI	Cortisol > 15 mcg/dl NORMAL
Hypoproteinemia (albumin < 2.5 g/dl):		
Cortisol < 8 mcg/dl POSSIBLE AI	Cortisol 8-11 mcg/dl CONSIDER AI	Cortisol > 11 mcg/dl NORMAL

AI: adrenal insufficiency

Glucocorticoid receptors

There are two isoforms of glucocorticoid receptors (GR) generated through alternative splicing. Alpha-GR (α -GR) is the main isoform and has mostly genomic actions, while beta-GR (β -GR) has negative dominant effect, counteracting α -GR actions⁶.

Critical illness induces a change in GR expression, favoring the β -GR isoform. This phenomenon explains the glucocorticoid resistance postulated for critical illness³⁰.

Hepatic GR activated by cortisol can regulate enzyme action and diminish its own catabolism³¹. Another important effect mediated by hepatic GR during critical illness is glucose homeostasis³²⁻³⁴.

During sepsis, GR are partially downregulated. Higher levels of cortisol, as part of high doses glucocorticoid treatment can further suppress hepatic GR, leading to hepatic inflammation, injury and increasing mortality³¹.

Bile acids

Besides its classical role in lipid absorption, bile acids have crucial functions in regulation of inflammation and endocrine homeostasis. Bile acids, like steroid hormones, are derivative products from cholesterol. Both metabolic pathways share enzymes and steps⁶.

For instance, the principal enzyme for cortisol catabolism, the 5-reductase, is pivotal for bile acids synthesis³⁴. Subsequently, enzymatic feedback due to bile acids increase during critical illness (10 times above normal), determinates diminished levels and activity of the enzymes and consequently, diminished cortisol catabolism^{12, 29}.

Bile acids interact with multiple nuclear receptors including GR³⁵. Given the high levels of bile acids in the context of critical illness³⁶, they are also able to cross the central nervous system barrier and inhibit HPAA at the hypothalamic level³⁷.

Possible scenarios in critically ill patients

Critical illness can affect individuals with previous diagnosis of adrenal insufficiency, either primary or secondary. On the other side, an unknown diagnosis of adrenal insufficiency due to lack of recognition or recent development of the disease, can be associated with adrenal hemorrhage, cranial traumatism, pituitary tumor or apoplexy³⁸.

Adrenal insufficiency can be triggered by drugs that interfere cortisol synthesis (e.g. etomidate, ketoconazole) or enhance its catabolism (e.g. phenobarbital, phenytoin, rifampicin), agents that inhibit central regulation (e.g. opioids) or due to abrupt withdrawal of glucocorticoids or drugs with agonist effects (e.g. megestrol). Anticoagulants can precipitate adrenal hemorrhage and consequently,

primary adrenal insufficiency. These situations should be taken into account while designing the clinical record²³.

Relative adrenal insufficiency or critical illness-related corticosteroid insufficiency (CIRCI)

The concept was proposed by Rothwell in 1991³⁹. It is defined as the inability of reaching an increment in cortisol > 9 mcg/dl during cosyntropin stimulation test during critical illness. The author suggested the prognostic relevance in patients with septic shock as marker of increased mortality.

It has been applied thereafter as indicator for glucocorticoid replacement need. On this matter, Annane et al, evaluated 299 patients with septic shock classified according to cosyntropin stimulation test response⁴⁰. Those who failed to respond (cortisol increase < 9 mcg/dl) were treated with hydrocortisone 50 mg every 6 hours associated with fludrocortisone 100 mcg daily. They reported that the treated group showed benefits in terms of mortality and shorter time to extubation. However, this study was hardly questioned as detailed below.

Evidence that refutes the existence of relative adrenal insufficiency or critical illness-related corticosteroid insufficiency (CIRCI)

The most sensitive issue is that pivotal studies have serious clinical and methodological limitations (treatment with etomidate in the responder group—a known steroidogenesis inhibitor—, high mortality in the placebo group and statistical methods used to report outcomes)²¹ added to the point of not considering physiological HPAA variations during critical illness.

There is opposed evidence. Widmer and cols. demonstrated that patients under major surgical stress with favorable outcome, showed a response to cosyntropin stimulation test < 9 mcg/dL, like one third of non-stressed healthy controls⁴¹.

The cosyntropin stimulation test, validated in non-stressed healthy population, lacks of reproducibility in critically ill patients, especially in those with septic shock^{26, 42}. Additionally, cortisol response in a HPAA maximally stimulated due to critical illness is expected to be reduced²¹.

Lower levels of carrier globulins in critical illness condition the elevation of cortisol in response to stimulus: critically ill patients with near normal protein levels showed greater cortisol response than patients with hypoproteinemia^{17, 23}. Furthermore, larger distribution volume adds variability^{1, 6}.

Diminished cortisol catabolism also impacts on reducing response to cosyntropin stimulation test^{12,19}. Elevated cortisol levels, decreased ACTH in response to feedback and adrenal tropism can influence test results²¹.

Some patients with partial central adrenal insufficiency can have a normal response to 250 mcg of cosyntropin and the 1 mcg test is not supported in this scenario²³.

Thus, it seems that cosyntropin stimulation test is not an appropriate test for evaluating HPAA in the critical illness context.

Evaluation of hypothalamic-pituitary-adrenal axis function during critical illness

Considering the alterations in cortisol regulation and metabolism and carrier protein levels, interpretation of cortisol levels in critically ill patients differs from healthy individuals. These limitations can lead to misinterpretation of the state of critically ill patients regarding adrenal sufficiency²¹.

The prevalence of adrenal sufficiency in critically ill patients has been reported between 0 and 77%. However, it is difficult to establish owing to the limitations of the evaluating tools, the differences among populations included in the studies and the diagnosis criteria applied⁴³.

A more reliable tool would be the measurement of serum free cortisol, nevertheless it is not available in clinical practice and cut-off values have not been established for critically ill patients. Salivary free cortisol has good correlation with serum free cortisol and reflects its changes rapidly. Notwithstanding, getting a sample can be challenging in critically ill patients²³.

As previously stated, cosyntropin stimulation test is not a valid test in critically ill patients, due to poor reproducibility in the context of high distribution volume (40% larger than normal) and decrease CBG levels among other factors^{8,12}.

These caveats also apply to the measurement of total cortisol, but thus far seems to be the most appropriate method for evaluating HPAA, taking into account the limitations in each case (protein levels, treatments that interfere synthesis, action, catabolism, etc.). As previously mentioned, due to the lack of circadian rhythm, random cortisol can be useful for diagnosis²¹ (Figure 2).

No other dynamic tests like insulin hypoglycemia, metyrapone test or CRH test are approved in critical illness²⁵.

Treatment

Since half-life of cortisol is prolonged in critical illness, actual recommendations, based in guidelines published in 2017⁴⁴, of doses ranging 200-400 mg of hydrocortisone per day seem to be excessive and long-term consequences are unknown⁶.

Under septic shock conditions, these doses have shown to reduce duration of vasoactive drug need and ventilation, due to anti-inflammatory effects, without a clear reduction of mortality^{40,45-47}. In fact, long-term use of high doses of glucocorticoids causes hepatic glucocorticoid receptor suppression with increasing inflammation and mortality³¹. The need and modality of treatment in the acute phase is still controversial, given the disparity of the data^{45,46}.

The newest meta-analyses confirm the minimal or absent mortality benefit of glucocorticoid treatment in patients with septic shock. Rygård et al included 7297 patients of 22 studies and found no improvement in short-term or long-term mortality in patients treated with glucocorticoids compared to placebo (relative risk of 0.98, 95% confidence interval 0.89-1.08 and 0.96, 0.91-1.02, respectively) but only a shorter duration of shock, mechanical ventilation and intensive care unit stay⁴⁸. Rochwerg et al. found similar results in a meta-analysis of 42 studies including 10 194 patients⁴⁹. Both groups report greater frequency of adverse events in the treated group (hypernatremia, hyperglycemia).

In those critically ill patients without septic shock whose cortisol levels suggest adrenal insufficiency, the proposed treatment is hydrocortisone 25 mg every 6 hours and rapidly decrease of the dose according to clinical outcomes. In the context of primary adrenal insufficiency, fludrocortisone 50-100 mcg should be added when doses of hydrocortisone are adjusted below 50 mg daily. In patients with septic shock, doses of hydrocortisone should be doubled (50 mg every 6 hours) followed by the same approach of rapid tapering of the dose according to clinical response²³.

On the other hand, the prolongation of critical illness beyond 4 weeks accompanied by a decrease in cortisol levels, is probably the time for starting physiologic replacement therapy, if not started before, because of persistent low ACTH levels that lead to structural and functional impairment of adrenal cortex⁸.

To conclude, diagnosis of adrenal insufficiency during critical illness can be troublesome. A high suspicion level should be present for patients at risk of adrenal insufficiency and the leading cause should always be assessed. Considering limitations of diagnostic methods in critically ill patients is of utmost importance. The cosyntropin stimulation test has no validity and is not needed for diagnosis.

Serum free cortisol is desirable but not available in clinical practice. Hence, serum cortisol is considered and interpreted according to carrier proteins.

The treatment with hydrocortisone, if needed, should not exceed 200 mg daily and be tapered as soon as possible to the physiological dose.

We discourage the concept of relative adrenal insufficiency or CIRCI and its treatment. Alternatively, we propose the concept of transient adaptative glucocorticoid

resistance induced by stress. Although there is no method to evaluate glucocorticoid sensibility, some evidence can support an increase in resistance: increased cortisol bioavailability (through cleavage of carrier proteins or decreased catabolism), differentiated expression of glucocorticoid receptors, among others.

Conflicts of interest: None to declare

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