CHAPTER 1.

General introduction and outline of the thesis

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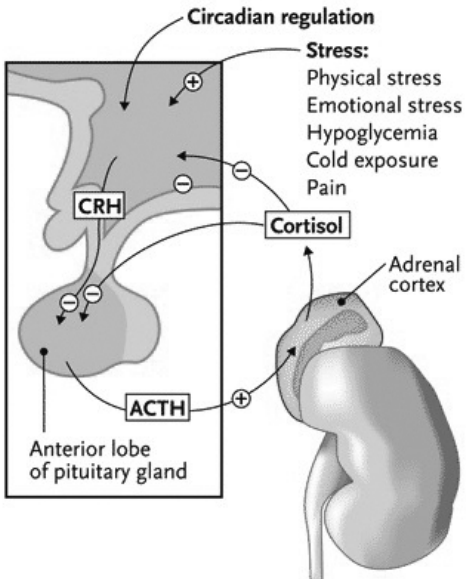
The adrenal gland and its role in the critically ill

The adrenal glands lie in the retroperitoneum above or medial to the upper poles of the kidneys. They weigh 8-10 grams only, but their function is crucial in surviving critical illness [1]. This thesis focuses on adrenal dysfunction in the critically ill.
Acute and chronic stressful events in life initiate a well-coordinated physiological response to maintain homeostasis. This stress response is primarily mediated by the hypothalamic pituitary adrenal (HPA) axis which is schematically visualized in figure 1 [2].

Figure 1 Schematic presentation of HPA axis [2]. ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone. Reproduced from Klemm D. Am Fam Phys. 2000;5:1119-1127, with permission.



Activation of the HPA axis results in increased secretion of corticotrophin-releasing hormone (CRH) by the hypothalamus, which stimulates the production of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland, causing the adrenal cortex to produce cortisol. In addition, the HPA axis and immune system are closely and bidirectionally integrated and thereby inflammatory cytokines may activate the HPA axis [3,4]. Other factors may also contribute to higher cortisol levels during critical illness. In 2013 Boonen et al. revealed that cortisol breakdown was substantially reduced during critical illness resulting in a fivefold longer half-life of cortisol leading to higher baseline cortisol levels [5]. The reduced cortisol breakdown was explained by suppressed expression and activity of cortisol metabolizing enzymes. Another factor contributing to high free cortisol concentrations involves the binding

characteristics of cortisol. Normally over 90% of cortisol is bound to binding proteins mainly corticosteroid binding globulin (CBG) and in lesser degree to albumin. The remaining cortisol is available in the unbound form which is biologically active. During critical illness levels of binding proteins may fall which may lead to an increase in the free cortisol fraction [6,7].
The biological effects of cortisol are extensive. Actions of cortisol include, but are not limited to, maintenance of glucose levels during fasting, anti-inflammatory effects on the immune system, as well as maintenance of vascular tone, endothelial integrity, increased sensitivity to vasopressors and reduction of induced nitric oxide mediated vasodilatation [8,9]. The essential role of cortisol for survival is best appreciated in patients with partial or complete deficiency of glucocorticosteroïds. In these patients stressful events may lead to vascular collapse and even death [1].

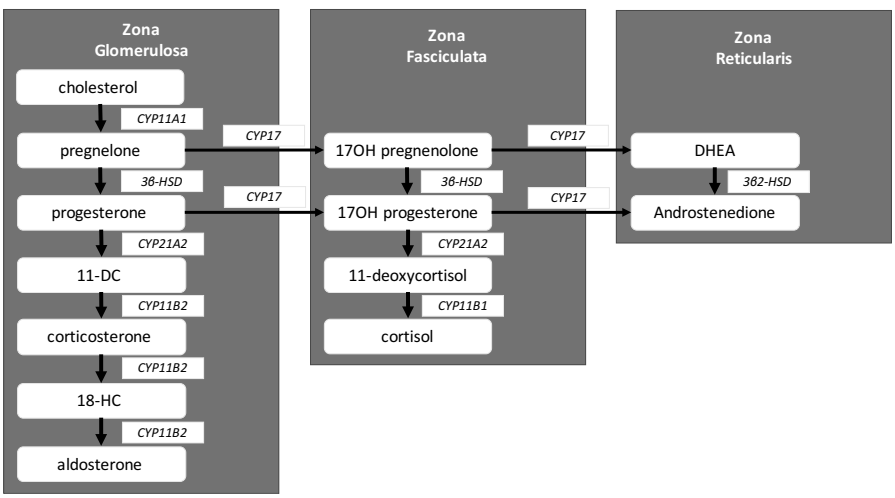
Critical illness related corticosteroid insufficiency (CIRCI)

Dysfunction of the HPA axis has increasingly been recognized during critical illness. The dysfunction can be seen in up to 60% of the critically ill patients with severe sepsis and especially septic shock. Dysfunction of the HPA axis can also be described in patients with severe community acquired pneumonia, trauma, burns, hepatic failure, pancreatitis and after major surgery as well as in the setting of injury or structural change to the hypothalamus, pituitary, or adrenal gland [3,10]. The entity of critical illness related corticosteroid insufficiency (CIRCI), its diagnosis and clinical implications, such as administering corticosteroids remain highly controversial. What is CIRCI and what is the pathophysiology of CIRCI ?
At the beginning of our research the adrenal dysfunction during critical illness was frequently described as either relative adrenal insufficiency or adrenal failure. Relative adrenal insufficiency referred to a state of insufficient cortisol levels for the severity of the illness of the patient manifested by a subnormal rise of the cortisol level in response to additional stimuli. In 2008 the International Task Force by the American College of Critical Care Medicine summarized the pathophysiologic changes to the HPA axis that occur during critical illness and the potential development of adrenal dysfunction that could result from these changes. They did not only describe adrenal dysfunction, but also inadequate corticosteroid activity due to corticosteroid resistance. The task force recommended to use the term critical illness related corticosteroid insufficiency or CIRCI to describe the complex syndrome referring to a state of inadequate corticosteroid activity for the severity of the illness of a patient [11]. The mechanisms leading to CIRCI are complex and poorly understood. In general the pathophysiological mechanisms may be divided into two categories: inadequate cortisol availability and corticosteroid resistance. These will be discussed below.

Inadequate cortisol availability

Inadequate cortisol availability is likely due to a decreased production of CRH, ACTH and cortisol. Decreased CRH and ACTH production has been reported due to subarachnoid haemorrhage or necrosis of the hypothalamus or pituitary gland and may result in decreased cortisol levels [12,13]. In addition, inflammatory cytokines such as TNF-α, have been shown to reduce cortisol synthesis by inhibiting the stimulatory actions of ACTH on adrenal cells [3]. Several mechanisms have been described to interfere directly with the synthesis of cortisol in the adrenal cortex. The synthesis of all steroid hormones begins with cholesterol. Various enzymatic steps ultimately lead to the production of cortisol. The synthesis of cortisol in the adrenal cortex is schematically visualized in figure 2. Possible mechanisms that may interfere with cortisol synthesis include impaired availability of steroidogenic enzymes or substrate deficiency (cholesterol) particularly in the course of sepsis and shock [14]. Furthermore, impairment of cortisol secretion may also develop when etomidate, a known inhibitor of 11β-hydroxylase promoting conversion of 11-deoxycortisol to cortisol, is used to facilitate intubation. The inhibition of the enzyme may last up to 72 hours [15,16].

Figure 2. Schematic presentation of steroidogenesis. 3BHSD: 3-hydroxysteroid-dehydrogenase; CYP21: 21-hydroxylase; 11-DC: 11-deoxycorticosterone; 18-HC: 18-hydroxycorticoterone; CYP11B1: 11ß-hydroxylase; CYP11B2: 11 & 18-hydroxylase; CYP17: 17-hydroxylase & 17,20-hydroxylase.



Also, structural changes to the adrenal gland such as adrenal haemorrhage or ischaemia may compromise adrenal function and this may result in long-term adrenal dysfunction [17]. Adrenal haemorrhage has been described in patients with blunt abdominal trauma,

after major surgery, in disseminated intravascular coagulation associated with sepsis, and in patients with burns, heparin-induced thrombocytopenia, the antiphospholipid syndrome, disseminated fungal infections, tuberculosis and Waterhouse Friderichsen Syndrome and may result in decreased cortisol secretion.

Corticosteroid resistance

In addition to changes at the level of cortisol availability to the tissues, critical illness is commonly associated with changes in the tissue sensitivity to glucocorticoids. Cortisol normally diffuses rapidly across cell membranes and binds to the glucocorticosteroid receptor. The glucocorticosteroid receptor complex (GR-complex) may move into the nucleus resulting in the actions of cortisol as previously described. Glucocorticoid resistance may be caused by an excessive cytokine production, as occurring during the overwhelming inflammatory response of septic shock. Cytokines such as TNF-α and IL-1β lead to a decreased affinity and / or density of glucocorticosteroid receptors for cortisol and other postreceptor alterations [3,8,18]. In these patients CIRCI may be present while (free) cortisol levels are appropriately elevated. Also, clinical and experimental data indicate that lack of improvement in patients with refractory sepsis and ARDS is frequently associated with a failure of the activated GR-complex to down-regulate the transcription of inflammatory cytokines, despite elevated levels of circulating cortisol. For instance, Meduri et al. demonstrated a markedly reduced nuclear density of the GR-complex in patients with acute respiratory distress syndrome (ARDS) who did not improve [19]. Although most research focuses on corticosteroid resistance in patients with sepsis and ARDS, it is likely that similar mechanisms leading to corticosteroid steroid resistance are present in other disorders characterized by significant systemic inflammation, including pancreatitis, burns, post-cardiopulmonary bypass, and liver failure.

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Diagnosis of CIRCI

CIRCI may produce a number of non-specific signs and symptoms and its diagnosis is challenging. Both clinical and biochemical signs can be used to diagnose CIRCI [20]. See table 2 for the summarized signs and symptoms of patients with CIRCI. The main clinical manifestation of CIRCI is hypotension that is poorly responsive to fluid challenges and/or vasopressor therapy especially in patients with a hyperdynamic hemodynamic profile [3,8].

Table 2. Signs and symptoms that raise the clinical suspicion of CIRCI

General	Fever (without apparent cause)
Haemodynamic	Hypotension poorly responsive to fluid challenges and/or vasopressor therapy especially in patients with a hyperdynamic profile
Mental	Weakness, fatigue, lethargy, agitation, apathy, depression without specific psychiatric disturbance, delirium, coma
Gastrointestinal	Anorexia, nausea, vomiting, diarrhoea, abdominal or flank pain
Laboratory	Hypoglycaemia, hyponatraemia, hyperkalaemia, hypercalcaemia, neutropenia, eosinophilia, hypothyroidism

CIRCI may be associated with a diminished adrenal responsiveness to additional stress, reflected by low cortisol levels given the severity of the illness and/or a diminished response to exogenous ACTH [9-21,22]. The latter is tested by the ACTH test: 250 μg of synthetic ACTH is given intravenously and serum total cortisol is assessed basally and 30 and 60 minutes after injection. CIRCI is usually defined by low increases of cortisol (<250 nmol/L) upon ACTH administration or by baseline cortisol values which are relatively low given the severity of the illness [3,8,21]. Opponents of the ACTH test question whether the test reliably reflects adrenal function and suggest that a diminished response to the ACTH test is merely a marker of severity of disease. Test results may also be confounded by significant variations in total cortisol plasma levels during the day and there are divergent trial results regarding reproducibility and assay variability of the ACTH test [23]. Moreover, because of a decline in CBG and albumin during critical illness a dissociation may occur between free and total cortisol and thereby confound the assessment of adrenal function [7, 24]. As described by Hamrahian et al., hypoalbuminemia may lead to a lower baseline total cortisol level while the biologically active free cortisol is appropriately elevated [6]. Since the measurement of free cortisol is arduous, complex and not widely available, formulas have been developed to estimate the free cortisol from total cortisol and CBG, including the Coolens equation

which estimates free cortisol by measuring total cortisol level and CBG and a fixed value for albumin [25]. Depending on studies and definitions, the incidence of CIRCI in the critically ill is estimated 20%, with an incidence as high as 60% in patients with severe sepsis and septic shock [3].

CIRCI and treatment with corticosteroids

In 1940 the first positive effects of treatment with corticosteroids were described for patients with adrenal dysfunction. Hans Seyle demonstrated that adrenalectomised animals exposed to shock had a high mortality rate, which could be ameliorated by treatment with corticosteroids [26,27]. Since 1940 multiple studies conducted the use of corticosteroids for patients with CIRCI, however its use in patients suspected of CIRCI is still hotly debated.

There is a general consensus that corticosteroids improve sepsis-associated comorbidities, such as shock and organ dysfunction. The positive effects of corticosteroids on cardiovascular function are explained by restoration in blood volume by sodium and water retention by binding to mineralocorticosteroid receptor in the kidney. Also, corticosteroids contribute to restoring systemic vascular resistance by enhancement of vascular contractility and increased sensitivity to vasopressors. The decrease in organ dysfunction can partly be explained by the anti-inflammatory effects of corticosteroids and the improvement of glomerular function, free water clearance and sodium renal excretion [28].

The effects of corticosteroids on survival and on the risk of secondary infections are controversial [29-35]. A pivotal randomized controlled trial by Annane et al. in patients with septic shock and a diminished response to ACTH testing showed significant shock reversal and reduction of mortality rate after administration of corticosteroids [29]. This finding was in line with previous studies demonstrating survival benefits of early hydrocortisone treatment in patients with septic shock independent of ACTH test results [30-34]. In contrast, in 2008 the results of the CORTICUS trial were published, a multicentre, randomized, placebo-controlled trial in which 499 patients with septic shock were included [35]. Patients underwent an ACTH test and were treated with corticosteroids or placebo. This study confirmed earlier shock reversal in the patients who were treated with corticosteroids. However, there was no significant reduction in 28-day mortality, regardless of the response to the ACTH test. Instead, patients receiving steroids showed an increased incidence of superinfections. Furthermore, since the breakdown of cortisol is substantially reduced during critical illness, Boonen et al. postulated that the current daily doses of 200 mg hydrocortisone is too high and will result in high circulating cortisol levels, and subsequently, a higher risk of side effects [36].

Nevertheless, the use of corticosteroids in clinical practice still remains controversial.

The results of the CORTICUS trial contributed to the downgrading of the use of ACTH testing and use of corticosteroids in the critically ill. In 2012 the Surviving Sepsis Campaign guidelines recommended not to use an ACTH test to identify the subset of adults with septic shock who should receive hydrocortisone. They recommend to consider a daily doses of 200 mg hydrocortisone treatment only in patients in whom adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability [37]. The recently revised guidelines are in line with the previous recommendation regarding the use of corticosteroids in patients with septic shock, however with more emphasis on not using corticosteroids if fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability [38,39].

Outline of the thesis

CIRCI is a complex syndrome and refers to a state of inadequate cortisol availability, due to adrenal dysfunction and corticosteroid resistance. In order to further unravel this syndrome we focused on assessing adrenal dysfunction in the critically ill. The thesis is divided in two parts. In part one we try to provide better insight in the complex pathophysiology of adrenal dysfunction during critical illness and diagnosis of CIRCI. In part two, we present our recommendations for diagnosing and treating patients with a clinical suspicion of CIRCI.

Part I Pathophysiology and diagnosis of CIRCI

In order to further understand the pathophysiologic mechanisms of CIRCI we investigated the adrenal response to ACTH during the course of critical illness in chapter 2. We studied whether a diminished adrenal sensitivity to endogenous ACTH (as defined by the cortisol/ACTH ratio), is associated with an attenuated response to exogenous ACTH (cortisol response to ACTH test), which may suggest adrenal dysfunction. Furthermore, we questioned whether the adrenal response to ACTH changes during the stage of the critical illness as suggested by Boonen et al. [5].

Etomidate, a drug that is used to facilitate intubation, interferes with the steroidogenesis of cortisol by suppressing the enzyme 11β hydroxylase. Other possible rate limiting steps in steroidogenesis during critical illness may contribute to the enrolment of CIRCI. In chapter 3, we present a novel approach to assess adrenal dysfunction during critical illness. We performed a prospective observational study measuring the precursors of cortisol to characterize the steroidogenesis of cortisol during critical illness in septic and non-septic critically ill patients. We also aimed to determine the impact of etomidate on the synthesis of cortisol. The results may help to gain insight into the pathophysiology of CIRCI.

Chapter 4 focuses on adrenal haemorrhage, a well-known but rare entity as a cause of adrenal dysfunction in critically ill patients. The characteristics of adrenal function testing in these patients are not well described since studies on adrenal haemorrhage are scarce and mostly comprise of case reports. We performed a systematic literature search to summarize the reported knowledge on adrenal function during adrenal haemorrhage confirmed by imaging techniques.

The diagnosis of CIRCI is challenging and laboratory tests can be used to assess adrenal function during critical illness. A dissociation between total and free cortisol may be present in the critically ill due to changes in binding proteins. The dissociation between total and free cortisol may confound the diagnosis of CIRCI if total cortisol is used to assess adrenal function. Furthermore, the regulation of binding proteins differs between septic and non-septic patients and subsequently the relation between free and total cortisol may be different. Chapter 5 addresses the question whether total cortisol reliably reflects free cortisol levels and whether this relation differs between septic and non-septic patients. We therefore performed a prospective study in critically ill septic and non-septic patients interrelating free and total cortisol. Since measurement of free cortisol is non-automated, laborious and not widely available, the aim of the prospective study in chapter 6 was to determine the agreement between calculated free cortisol levels according to the widely applied Coolens equation and the adjusted Södergård equations with measured free cortisol levels in the critically ill.

Part II Recommendations for daily practice

The purpose of the narrative review in chapter 7 was to elaborate on the pros and cons of treatment with corticosteroids in patients with septic shock in clinical practice and to formulate research directions. Furthermore, we designed a protocol concerning CIRCI for daily practice, published as a chapter in the Spanish ICU protocol book, “Cuidados Criticos” translated “Critical Care Medicine”. This book will soon be published in English as well. In chapter 8 we present the English version of this protocol.

Finally, in chapter 9, the previous chapters are summarized and discussed, and future perspectives are presented.

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