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ESSENTIALS Critical illness, an extreme form of severe physical stress, is charac- terized by important endocrine and metabolic changes. The devel- opment of critical care medicine has made possible survival from conditions that were previously rapidly fatal, and as a result many patients now enter a prolonged phase of chronic or persistent crit- ical illness. Acute endocrine adaptations are directed towards providing en- ergy and substrates for the vital fight or flight response in the context of exogenous substrate deprivation. Distinct endocrine and meta- bolic alterations characterize the chronic phase of critical illness, which seems to no longer be solely beneficial and may hamper re- covery and rehabilitation. The hypothalamus-anterior pituitary axes respond to critical illness in a bi-phasic manner, or a tri-phasic manner if recovery is included as the third ‘phase’. Onset of the stressful event causes an acute activation of pulsatile hormonal release from the anterior pitu- itary, followed by suppression in the chronic phase of illness, ultim- ately resolving to normality if recovery occurs. Thyroid function—plasma concentrations of triiodothyronine (T3) are acutely lowered and plasma concentrations of reverse T3 (rT3) increase. When patients remain critically ill for several weeks, the low plasma T3 concentration coincide with low T4 concentration and low or low-normal thyroid-stimulating hormone concentra- tion. The acute ‘low T3 syndrome’ is likely an adaptive response to fasting, but the low T4 and T3 levels during the prolonged phase of critical illness are likely to be at least partially maladaptive. Whether interventions to normalize T4 and T3 levels produce clinical benefit remains unproven. Adrenal function—during critical illness, increased cortisol (achieved by reduction in the breakdown of cortisol and decrease in plasma cortisol binding globulin levels) is considered to prioritize energy pro- vision to vital organs via its catabolic effects on metabolism and by switching off anabolism. ‘Relative adrenal failure’ is frequently treated with hydrocortisone (200–300 mg per day), but whether such high doses are needed has not been well investigated. Blood glucose control—the endocrine response to severe illness is assumed to guarantee availability of glucose for those

organs and tissues that rely on this as metabolic substrate. Hyperglycaemia in critically ill patients has a J-shape association with risk of death, with the lowest risk in patients who remain normoglycaemic. Following recent clinical trials targeting normoglycaemia is not currently re- commended for general daily clinical practice, but not tolerating pronounced hyperglycaemia has become the standard of care. Introduction The term ‘critical illness’ refers to any life-threatening condition re- quiring support of vital organ functions to prevent imminent death. Critical illness can be evoked by a variety of insults including mul- tiple trauma, complicated surgery, sepsis, and other severe medical illnesses. Critical illness is thus an example of pronounced physical stress, and all the immediate biological responses evoked by other stressful events are assumed to be of a greater magnitude in critic- ally ill patients. These immediate stress responses comprise orches- trated endocrine and metabolic adaptations that are presumed to be directed towards providing enough energy for the ‘fight or flight’ response in a context of temporary food deprivation. Alterations within the different hypothalamic-pituitary axes generate a ‘cata- bolic’ effect, in order to provide metabolic substrates, and to pri- oritize energy consumption for those processes essential for acute survival. With modern intensive care, survival from previously rapidly fatal conditions is now possible. However, full recovery is often not rapid and, when the triggering event has resolved, patients enter a chronic phase of critical illness during which they can re- quire vital organ support for weeks. This chronic phase is charac- terized by distinct endocrine and metabolic alterations which may no longer be solely beneficial and could potentially hamper re- covery. Recovery means renewal of cells that have a fast turnover, such as most epithelial and blood cells. For cells with a long half- life, such as neurons and myofibers, recovery requires removal of intracellular damage. This chapter summarizes recent insights with a specific focus on the hypothalamus-pituitary-thyroid and hypothalamus-pituitary- adrenal axes, the role of fasting in the acute stress response, and the impact of the hyperglycaemic response on recovery from critical illness. 17.9 Metabolic and endocrine changes in acute and chronic critical illness Eva Boonen and Greet Van den Berghe

17.9 Metabolic and endocrine changes 3907 Hypothalamic-pituitary axes The hypothalamus-anterior pituitary axes respond to critical illness in a bi-phasic manner, or a tri-phasic manner if recovery is included as the third ‘phase’ (Fig. 17.9.1). Onset of the stressful event causes an acute activation of pulsatile hormonal release from the anterior pituitary, followed by suppression in the chronic phase of illness, ultimately resolving to normality if recovery occurs. Although the concept applies to all hypothalamus-pituitary axes, recent studies have focused on the hypothalamus-pituitary thyroid axis and the hypothalamus-pituitary adrenal axis. The hypothalamus-pituitary-thyroid axis Responses to acute and prolonged critical illness Acute illnesses have an immediate effect on circulating thyroid hor- mone levels (Fig. 17.9.2). Plasma concentrations of triiodothyronine (T3) are acutely lowered and plasma concentrations of reverse T3 (rT3) increase, due to an immediate inactivation of thyroid hormone in peripheral tissues such as the liver, mediated by a suppressed activity of the type-1 deiodinase (D1) and/or an activated type-3 deiodinase (D3) (Fig. 17.9.2). In contrast, plasma concentrations of thyroxine (T4) and thyroid-stimulating hormone (TSH) increase briefly after onset of acute surgical stress. Thereafter, plasma TSH and T4 con- centrations return to ‘normal’. This constellation of low plasma T3 concentrations and elevated rT3 is referred to by different names: the acute low-T3 syndrome, the euthyroid-sick syndrome, or the non- thyroidal illness syndrome. There are several candidate mediators of this acute decrease in plasma T3 concentrations including cytokines, hypoxia-triggered signalling, and lack of nutrition. Acute reduction in the plasma concentrations of thyroid hormone binding proteins

and the inhibition of hormone binding, transport, and metabolism by ele- vated free fatty acid and bilirubin concentrations also play a role. When patients remain critically ill for several weeks the alterations within the thyroid axis become different. In this phase of critical illness, low plasma T3 concentration coincide with low T4 concentration and low or low-normal TSH concentration (Fig. 17.9.2). Moreover, the pulsatility of TSH secretion is largely lost and reduced pulsatile TSH secretion correlates with low plasma thyroid hormone concentra- tions, a constellation that resembles central hypothyroidism (Fig. 17.9.2). In line with central hypothyroidism postmortem studies demonstrate suppressed expression of thyrotropin-releasing hor- mone (TRH) gene in the hypothalamic paraventricular nuclei. Suppressed expression of the TRH gene correlates positively with the low plasma concentrations of TSH and T3. Thus, in prolonged critical illness, the production and release of thyroid hormones from the thyroid gland appears reduced due to diminished hypothalamic stimulation of the pituitary thyrotropes. Recovery is preceded by hypothalamus-pituitary reactivation with an increase in TSH levels followed by an increase in thyroid hormone concentrations. The mechanisms underlying suppressed hypothalamic TRH ex- pression during prolonged critical illness are incompletely under- stood. There appears to be a ‘resetting’ of the set point for feedback inhibition, via a local increase in type-2 deiodinase (D2) activity in the hypothalamus, which could elevate local thyroid hormone levels. Local cytokine effects within the hypothalamus, but also effects of endogenous dopamine or cortisol may play a role. Additionally, during prolonged critical illness peripheral tissues respond to low T3 levels by mechanisms capable of increasing local hormone avail- ability and effects. The monocarboxylate transporters, responsible for thyroid hormone uptake, were are overexpressed in skeletal muscle, liver, and kidney during prolonged critical illness (Fig. 17.9.3). The upregulation of these transporters is reversible by thy- roid hormone treatment. D2-expression and activity is upregulated in skeletal muscle and upregulation of D2 in the lung is an adap- tive response to lung injury. At the level of the thyroid hormone re- ceptor (TR), an inverse correlation is observed between the ratio of active TR-1 over inactive TR-2, a surrogate marker of thyroid hor- mone sensitivity, and the T3/rT3 ratio in liver biopsies of prolonged critically ill patients. Together, the available evidence suggest that in prolonged critical illness, the production of thyroid hormones falls whereas peripheral tissues protect themselves by increasing thyroid Acute phase Chronic phase Recovery phase Normal level Serum concentration or secretion Cortisol Anterior pituitary hormones Target-organ hormones Fig.17.9.1 Schematic overview of the pituitary-dependent changes during the course of critical illness. In the acute phase of illness, the secretory activity of the anterior pituitary is essentially maintained or increased, whereas anabolic target organ hormones are suppressed. Catabolic cortisol levels are elevated presumably driven by a brief increase in adrenocorticotropic hormone (ACTH). In the chronic phase of critical illness, the secretory activity of the anterior pituitary appears uniformly suppressed coinciding with reduced circulating levels of target organ hormones. Cortisol is a notable exception, the circulating levels of which remain elevated because of suppressed breakdown. Figure reproduced from Van den Berghe G, de Zegher F, Bouillon R (1998). Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab, 83(6), 1827–34.

 hormone transporters, local activation of thyroid hormone and gene expression of the active TR isoform. What are the consequences of low plasma T3 concentrations in protracted critical illness? Low T3 levels correlate inversely with markers of muscle breakdown and of bone loss in prolonged critic- ally illness. This correlation may reflect

either an adaptive and pro- tective response against catabolism or a causal maladaptive reaction. As the cause of the low thyroid hormone levels is suppressed ex- pression of TRH in the hypothalamus, the optimal way to address the question of causality is by assessing the effect of TRH treatment. A continuous infusion of TRH can increase plasma T4 and T3, but also increases rT3 concentration. However, when TRH is combined with a growth hormone (GH)-secretagogue, no rT3 increase occurs which was explained by a GH-mediated suppressive effect on the inactivating D3 enzyme. As this treatment also induces an anabolic response during prolonged critical illness, it can suggest a causal relationship between low thyroid hormone levels and impaired an- abolism in chronic critical illness. Treatment with releasing factors has the advantage that negative feedback inhibition by thyroid hor- mones on thyrotropes is maintained, and thus overstimulation of the thyroid axis is prevented. Diagnostic implications The changes that occur within the thyroid axis during critical illness complicate the diagnosis of pre-existing thyroid disease. Indeed, patients with pre-existing primary hypothyroidism would nor- mally have high plasma TSH concentrations, but when primary hypothyroidism and severe nonthyroidal critical illness coincide, even more so when iatrogenic factors such as treatment with dopa- mine are involved, TSH levels may be lower than anticipated, even completely suppressed. Hence a low TSH during critical illness does not exclude the presence of primary hypothyroidism. As the low T4 and T3 levels in patients with severe hypothyroidism and crit- ical illness can be indistinguishable from those values observed in prolonged nonthyroidal critical illness, this further complicates such a diagnosis. Repeated thyroid function tests after recovery are re- quired to confirm a suspected diagnosis of thyroid disease. Elevated plasma T4 and T3 concentrations are so unusual during critical illness that they should always raise concern about pre-existing hyperthyroidism. The undetectable TSH expected with primary hyperthyroidism loses all diagnostic value during critical illness. Therapeutic implications The currently available evidence suggests that the acute ‘low T3 syn- drome’ is likely an adaptive response to fasting. Hence, it is highly unlikely that treatment would be beneficial. In contrast, the low T4 and T3 levels during the prolonged phase of critical illness are likely to be at least partially maladaptive. Indeed, in prolonged crit- ical illness in patients who are receiving nutrition, the low T3 syn- drome can be reversed by infusion of hypothalamic releasing factors leading to an anabolic response. However, no studies have yet inves- tigated the effect of such treatment on morbidity and mortality and the clinical implications of these experimental findings are currently unclear. Normalizing plasma concentrations of thyroid hormones by treatment with T4 and/or T3 has proven very difficult during crit- ical illness. While a high dose of T4 could normalize plasma T3 con- centrations it may result in supranormal T4 levels and even higher rT3. A high dose of T3 can normalize plasma T3 but suppresses TSH and T4 to subnormal levels via negative feedback inhibition. In com- bination, the risk of overtreatment is even higher. It remains equally controversial when and how to treat primary hypothyroidism during critical illness. It appears common sense to TRH Hypothalamus Pituitary Plasma levels & tissue metabolism Peripheral tissue level & effects TSH TSH secretion pulsatile pattern diurnal rhythm Healthy subjects Critical illness T4 T2 T3 rT3 Binding proteins & binding Peripheral TH uptake TR expression D1, D2 D1, D2 D3 D3 TRH Acute phase Chronic phase TRH Plasma TSH ↑/ = Pulsatility = No diurnal rhythm Normal TRH expression Binding proteins & binding ↓ Peripheral TH uptake ↓ TR expression ? T4↑/ = T2 T3↓ rT3↑↑ D1↓ D2 = D1↓ D2 = D3↑ D3↑ 0 7 21h 06h TSH (mU/l) TRH expression ↓ Plasma TSH ↓ Pulsatility ↓↓ No diurnal rhythm 21h 06h Binding proteins & binding = Peripheral TH uptake ↑ TR expression ↑ T4↓↓ T2 T3↓↓ rT3↑= D1↓ D2↑ D1↓ D2↑ D3↑ D3↑ Fig.17.9.2 Simplified changes in the central and peripheral components of the hypothalamic-pituitary- thyroid axis during acute and prolonged critical illness, as compared with healthy status.

17.9 Metabolic and endocrine changes 3909 continue the maintenance dose of thyroid hormone for patients who were receiving this treatment prior to critical illness. When a patient presents with myxedema coma, it is current practice to administer parenteral thyroid hormone. For this endocrine emergency, many clinicians prefer an IV loading dose of 300–500 μg of T4 to quickly reach 50% of the euthyroid value of T4, followed by 50–100 μg of IV T4 daily until oral intake is possible. Some experts have suggested the use of a coinfusion of T3 with T4. Whether and how symptom- atic patients with low T3 and T4 during prolonged critical illness, but without a proven history of hypothyroidism, should be treated remains unknown. The experimental protocol of the author's insti- tution advises administering one 100–150 μg bolus of T4 intraven- ously per 24 hours alone or, when required to also increase plasma T3, combined with T3 at 0.6 μg/kg ideal body weight per 24 hours by continuous intravenous infusion, adapting the dose based on clinical assessment, frequent monitoring, and targeting serum thy- roid hormone levels in the low-normal range. When patients start to recover, a prompt tapering of this dose is usually required. The need for treatment of primary hyperthyroidism may also be affected by concomitant critical illness. Indeed, theoretically, treatment re- quirements could be lower as thyroid hormone metabolism is high during critical illness. Furthermore, when patients are receiving ac- tive treatment for hyperthyroidism when becoming critically ill, po- tential toxicity of the medication and interaction with other drugs should be taken into account. The hypothalamus-pituitary-adrenal axis The response to acute and prolonged critical illness Cortisol is the stress hormone, considered to be a key player in the 'fight or flight' reaction to illness and trauma. It is generally accepted that all types of stressful events activate the hypothalamic-pituitary- adrenal (HPA) axis via the hypothalamic release of corticotropin- releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the anterior pituitary corticotrophs to secrete adrenocor- ticotropic hormone (ACTH) (Fig. 17.9.4). During critical illness, in- creased cortisol is considered to prioritize energy provision to vital organs via its catabolic effects on metabolism and by switching off anabolism. Also, cortisol optimizes the haemodynamic response to severe illnesses by intravascular fluid retention and by enhancing inotropic and vasopressor effects of catecholamines and angiotensin II. Furthermore the anti-inflammatory properties of cortisol prevent excessive inflammation in response to critical illness. Traditionally, it is assumed that a several-fold increased produc- tion rate of cortisol in the adrenal cortex, driven by high circulating ACTH, brings about the elevated plasma cortisol concentrations during critical illness. However, most studies could not document elevated plasma ACTH concentrations in critically ill patients, ex- cept very transiently. In a recent study, plasma ACTH concentra- tions were suppressed, in the face of high plasma cortisol, from the first day in the intensive care unit (ICU) and remained lower than normal throughout the first week of critical illness. Low plasma ACTH in the presence of high plasma cortisol concentrations has been interpreted as non-ACTH-driven cortisol production, in which direct adrenocortical effects of cytokines could play a role. However, no study had ever provided direct evidence for an increased cor- tisol production during critical illness. Recent work that used a state of the art cortisol tracer technique showed that daytime cortisol production during critical illness was only slightly higher or equal to that of healthy subjects (Fig. 17.9.5). Even more surprisingly, nocturnal cortisol secretion rates were found to be lower than in matched healthy subjects. In a recent study cortisol breakdown was found to be substantially reduced, attributable to suppressed expres- sion and activity of A-ring reductases in the liver and by suppressed activity 11β-hydroxysteroid dehydrogenase type 2 in kidney. The exact cause of the suppression of these enzymes remains unclear, but data point to a possible role of bile acids, which are elevated during critical illness and potent inhibitors of the cortisol metabolizing en- zymes (Figs. 17.9.4 and 17.9.5). The concept of

increased bioavailability of cortisol during the stress of severe illnesses via reducing its breakdown, can be inter- preted as a highly ‘cost-effective’ way to maintain increased cortisol Human patients Rabbit model Plasma hormone concentrations Tissue expression 2.0 ∗ TT3 (nmol/l) 1.5 1.0 0.5 0.0 160 ∗ 120 80 40 0 TT4 (nmol/l) Liver Muscle MCT8 mRNA 2.0 3.0 1.0 0.0 ∗ ∗ MCT10 mRNA 2.0 3.0 1.0 0.0 2.0 3.0 1.0 0.0 ∗ ∗ 2.0 3.0 1.0 0.0 ∗ 2.0 MCT8 mRNA 1.5 1.0 0.5 0.0 ∗ 12 10 8 6 4 2 0 ∗ ∗ Fig.17.9.3 The upper panel represents the circulating thyroid hormones in acutely stressed (light blue bars, n = 22) and chronically ill patients (dark blue bars, n = 64). The white horizontal bars indicate the normal ranges. The central panel shows the relative monocarboxylate (MCT8 and MCT10) mRNA expression levels measured in liver and skeletal muscle of acutely stressed (light blue) and chronically ill (dark blue) patients. The lower panels show the relative expression levels of MCT8 and MCT10 in liver and muscle of healthy control rabbits (white bar), saline treated prolonged ill rabbits (light blue), and T3+T4 treated (dark blue bar) ill rabbits. Data are expressed as mean ± s.e.m. *p <0.05 versus acute values. Figure reproduced from Boonen E, Van den Berghe G (2014). Endocrine Responses to Critical Illness: Novel Insights and Therapeutic Implications. J Clin Endocrinol Metab, 99(5), 1569–82. Copyright © 2014, by permission of Oxford University Press.

Section 17 Critical care medicine 3910 Fig. 17.9.4 Simplified cartoon of the changes in the hypothalamus-pituitary-adrenal axis during critical illness, as compared with during health. Figure adapted from Boonen E, Bornstein SR, Van den Berghe G (2015). New insights into the controversy of adrenal function during critical illness. Lancet Diabetes Endocrinol, 3(10), 805–15, copyright © 2015, with permission from Elsevier. Fig. 17.9.5 Panel (a) depicts cortisol production in critically ill patients with the systemic inflammatory response syndrome (SIRS) (N = 7; dark blue bar) and no systemic inflammatory response syndrome (N = 4; light blue bar) compared to controls (N = 9; white bar). Based on these results, 24 h cortisol production (mg/day) was estimated and depicted with the arrows. Panel (b) depicts cortisol plasma clearance as assessed with a small dose of deuterated cortisol tracer. Bar charts represent means and standard errors. Panel (c)-(e) show mRNA and protein expression of 5β-reductase in liver of 20 controls (white bar) and 44 patients (blue bar) and the relation to plasma total bile acid concentrations. Bar charts represent means and standard errors. The mRNA data are expressed, normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH), as a fold difference from the mean of the controls. Protein data are expressed normalized for CK-18 protein expression, as a fold difference from the mean of the controls. Figure reproduced from Boonen E, Van den Berghe G (2014). Endocrine Responses to Critical Illness: Novel Insights and Therapeutic Implications. J Clin Endocrinol Metab, 99(5), 1569–82. Copyright © 2014, by permission of Oxford University Press.

17.9 Metabolic and endocrine changes 3911 levels and to prioritize the consequences thereof to those tissues and cells that produce the metabolizing enzymes. Other cost-effective mechanisms are low plasma cortisol binding globulin levels in crit- ical illness, causing increased levels of biologically active free cortisol, and possibly tissue-specific effects, regulated at the level of gluco-corticoid receptor (GR) expression. GR expression is suppressed in white blood cells of critically ill children, which may safeguard an effective innate immune response and protect the host against in- fections in the presence of hypercortisolism, the latter generating its effects primarily in those tissues with a normal or perhaps even increased GR expression. This novel concept of tissue-specific regu- lation of glucocorticoid activity during critical illness requires fur- ther investigation. The new insight that during critical illness cortisol metabolism is suppressed could explain low

plasma adrenocorticotropic hormone concentrations via negative feedback inhibition at the level of the pituitary gland and/or the hypothalamus, but studies assessing this at the tissue level are currently lacking. Post-mortem studies in pa- tients after prolonged critical illness demonstrate clear signs of im- paired adrenocorticotropic hormone signalling in the adrenal gland. It is thus possible that sustained suppression of ACTH secretion causes adrenal atrophy in the prolonged phase of critical illness. This would explain the reported 20-fold higher incidence of symptomatic adrenal insufficiency in critically ill patients being treated in the in- tensive care unit for more than 14 days. Diagnostic implications Fifteen years ago, the term ‘relative adrenal insufficiency’ was launched in the context of critical illness. The term refers to the con- dition of a critically ill patient, in which, despite a maximally ACTH- activated adrenal cortex, cortisol production is still insufficient to generate enough glucocorticoid and mineralocorticoid receptor ac- tivation to safeguard hemodynamic stability. The large association studies pioneering this concept suggested that this condition is iden- tifiable by an insufficient increase (<9 μg/dl: 250 nmol/l) in plasma cortisol following a bolus injection of 250 μg ACTH, irrespective of the baseline plasma cortisol concentration, which is usually much higher than in healthy humans. In such a condition of insufficiently increased cortisol production, a very high plasma ACTH concen- tration would be expected. However, the recent robust finding that ACTH plasma concentrations are suppressed rather than increased, that cortisol production rate is not much elevated if at all, and that instead reduced cortisol breakdown plays a major role during crit- ical illness, further complicates the issue of diagnostic criteria for ad- renal failure in this setting. Moreover, in critically ill patients cortisol responses to a bolus of ACTH correlate positively with both cor- tisol production rate and with cortisol clearance. Patients who have the lowest cortisol response to ACTH, below the level that is seen in patients suffering from absolute adrenal failure, are those with the most suppressed cortisol breakdown while their plasma cortisol levels are identical to those with a higher response to adrenocor- ticotropic hormone. These findings suggest that a low cortisol re- sponse to an ACTH injection during critical illness mostly reflects the degree of negative feedback inhibition exerted by high levels of circulating cortisol, a finding that is quite similar to what is ob- served in patients treated with exogenous glucocorticoids for an extended time. Whether this low cortisol response to adrenocor- ticotropic hormone during critical illness also indicates that cortisol availability would be ‘insufficient’ to cope with the stress of illness, and thus requires treatment with corticosteroids, remains highly debated. Furthermore, circulating total cortisol concentrations do not necessarily reflect the amount of glucocorticoid effect. Evidence from both animal and human experiments suggests that there is tissue-specific regulation of glucocorticoid receptor expression during critical illness, thus conclusions about ‘adequacy’ of cortisol availability and function are not easily drawn from measurements of plasma cortisol concentration. Therapeutic implications It is standard practice for patients with an established diagnosis of primary or central adrenal failure, or patients treated with systemic glucocorticoids prior to critical illness, to be treated with supple- mental ‘stress doses’ of hydrocortisone, commonly 200–400 mg/ day. Also, patients suffering from an acute Addisonian crisis in the ICU are treated with high doses of corticosteroids. However, this therapeutic strategy is based on the assumption of a several-fold in- creased cortisol production during critical illness and whether such high doses are truly needed and whether lower doses may suffice with fewer side effects has not been well investigated. The dose of hydrocortisone currently recommended to treat ‘relative adrenal failure’ is controversial. The proposed dose of 200–300 mg of hydrocortisone per day, referred to as ‘low dose’ in the literature, in fact represents approximately 10-times more than that produce by a healthy human per day, and about three to six times more than the production which has now been quantified in critically ill patients (Fig.

17.9.5). In view of the substantially re- duced cortisol breakdown during critical illness, these doses may be too high and it is unclear for how long such a treatment should be given. During critical illness treatment with corticosteroids in a too high dose for too long time could contribute to lean tissue wasting, to my- opathy and prolonged need for intensive care. Based on the results of stable isotope studies, a dose of +/-60 mg of hydrocortisone, equiva- lent to about a doubling of the normal daily cortisol production, may be sufficient and merits further investigation. In all cases, tapering to the lowest effective dose as soon as the patient has been stabilized is advisable to limit side effects. The role of fasting in the acute stress response Critically ill patients cannot feed normally by mouth and establishing full feeding by the enteral route takes time and generally results in a substantial macronutrient deficit. Until recently, it was unclear what part of the acute endocrine/metabolic stress response is brought about by this obligatory fasting, and to what extent the coupling be- tween the responses to the stressful event and those to the lack of food may affect recovery. Fasting and the hypothalamus-pituitary-thyroid axis response to critical illness In healthy subjects, the low plasma T3 concentrations induced by fasting have been shown to mediate adaptive, beneficial effects counteracting the catabolic consequences of lack of macronutrients. Whether or not the acute decrease in circulating levels of thyroid hormone in response to critical illness is brought about by lack of

 macronutrients and also reflects an adaptive attempt to reduce en- ergy expenditure, in which case it should be left untreated, was not clear. A recent large randomized controlled trial (RCT) investigated the impact of adding early parenteral nutrition to supplement en- teral feeding to reach normal nutritional targets as compared with tolerating the pronounced macronutrient deficit that accompanies enteral feeding alone. This trial provided indirect evidence that the acute low T3 syndrome of acute critical illness is an adaptive re- sponse as the patients who received intravenous nutrition in the acute phase of their critical illness had worse rather than improved outcome. Furthermore, the increase in T3 and in the ratio of T3 over rT3 with early forceful feeding explained statistically the worsening of the clinical outcome. These data thus suggest that at least part of the acute decrease in T3 concentration during critical illness is evoked by the concomitant fasting and that this part of the low T3 syndrome is likely adaptive and beneficial. Possible benefits include the expected reduction in energy expenditure but also the direct ef- fect of increased D3 activity locally in granulocytes could optimize bacterial killing. Fasting and the hypothalamus-pituitary-adrenal axis response to critical illness Given the catabolic effects of increased cortisol availability, and the possible role of bile acids in mediating hypercortisolism during critical illness, an interaction between the HPA axis stress response and macronutrient availability is possible. Although eating and the infusion of glucose tend to increase plasma cortisol, more pro- longed caloric restriction activates the HPA axis. Hence, tolerating macronutrient deficit early during critical illness could evoke higher plasma ACTH and cortisol concentrations and early administra- tion of nutrition during critical illness may suppress this response and increase the need for steroid treatment. In the recent RCT dis- cussed here, intravenous administration of macronutrients did not affect the suppressed plasma concentration of ACTH or the elevated plasma cortisol concentration. The impact of hyperglycaemia on recovery from critical illness Association between high blood glucose and poor outcome of critical illness In humans, the endocrine response to severe illness is assumed to guarantee availability of glucose for those organs and tissues, such as the brain and the blood cells, which rely on glucose as metabolic sub- strate. In young and lean acutely ill patients, who do not suffer from comorbidities such as diabetes and are not receiving macronutri- ents or glucocorticoids, this stress response will

maintain normogly- caemia. However, when patients are older, overweight, suffer from chronic comorbidity, receive drugs that affect insulin sensitivity and receive enteral/parenteral nutrition, circulating glucose concentra- tion usually increases quickly above the upper limit of normality. In the condition of prolonged critical illness, hyperglycaemia may be quite severe and persistent. Hyperglycaemia in critically ill pa- tients has a J-shape association with risk of death, with the lowest risk in patient who remain normoglycaemic. In critically ill patients with established diabetes mellitus the J-shaped curve is significantly blunted in the hyperglycaemic zone and the nadir is shifted to higher blood glucose levels. This hyperglycaemia of critical illness could be adaptive or maladaptive. Hyperglycaemia and adverse outcome of critical illness: cause or consequence? Determining whether treating hyperglycaemia is beneficial or harmful during critical illness has been investigated in several RCTs. The first RCT on blood glucose management was performed in an adult surgical ICU in Belgium. In this study patient were randomly assigned a blood glucose target of strictly normal fasting blood glucose, (80–110 mg/dl, 4.4–6.1 mmol/litre) or contemporaneous usual care which was to tolerate hyperglycaemia up to 215 mg/dl (11.9 mmol/litre). The study was highly standardized, resulting in a strong internal validity. Targeting strict normoglycaemia reduced ICU and in-hospital mortality and reduced morbidity by preventing organ failure. In a second study using the same targets in the medical ICU of the same hospital, these morbidity benefits were confirmed, although mortality was not significantly affected. The same inves- tigators subsequently assigned critically ill children to a target of normal fasting glucose concentration for age, compared with toler- ating hyperglycaemia up to 215 mg/dl (11.9 mmol/litre), and found that targeting normoglycaemia reduced ICU morbidity and mor- tality and had long-term beneficial effects on neurocognitive devel- opment. Other investigators reported that targeting an adult range for fasting blood glucose in young infants in the ICU did not alter blood glucose concentration or patient outcomes. These results sug- gest that targeting the ‘normal’ fasting level for blood glucose may be key to prevent acute toxicity of hyperglycaemia during illness in each age group. The underlying mechanisms of hyperglycaemia- induced toxicity may involve cellular damage in those cells that do not require insulin for glucose uptake, such as hepatocytes, renal tubular cells, the endothelium, immune cells, and neurons. Soon after the first Belgian study was published, the interven- tion was swiftly implemented in clinical practice worldwide. After several smaller studies, a large multicentre international study compared tight blood glucose control to a normoglycaemic target (4.5–6.0 mmol/litre) with an intermediate target of less than 10.0 mmol/litre. This study reported that targeting normoglycaemia increased mortality. As this pragmatic trial had high external val- idity, targeting normoglycaemia is not currently recommended for general daily clinical practice. However, not tolerating pronounced hyperglycaemia has become the standard of care. Additionally, it now seems clear that targeting a narrow range for blood glucose requires accurate tools to measure blood glucose and that training and experience is crucial to avoid (undetected) episodes of hypogly- caemia. Profound, prolonged/undetected hypoglycaemia can have serious consequences and may result in death. How to deal with hyperglycaemia in clinical practice? With the available technologies, tight blood glucose control cannot be recommended for every ICU. Post-hoc analyses of the Belgian studies revealed that most of the benefit for mortality, to be achieved by blood glucose control, comes from avoiding excessive hyperglycaemia (Fig. 17.9.6). Thus, avoiding excessive hyperglycaemia and targeting blood glucose to +/-150 mg/dl (c.8 mmol/litre) is a reasonable com- promise. In a highly standardized environment, more can be gained by further tightening the glycaemic control, but it requires a substantial investment in training and technology to do this safely. Additionally,

17.9 Metabolic and endocrine changes 3913 avoiding early parenteral nutrition improves outcomes and reduces the requirement of insulin to prevent hyperglycaemia. Hence, to what extent forceful feeding contributes to the toxicity of hyperglycaemia during critical illness also requires further investigation. FURTHER READING Annane D, et al. (2002). Effect of treatment with low doses of hydro- cortisone and fludrocortisone on mortality in patients with septic shock. JAMA, 288, 862–71. Boonen E, et al. (2013). Reduced cortisol metabolism during critical illness. N Engl J Med, 368, 1477–88. Boonen E, et al. (2014). Impact of duration of critical illness on the adrenal glands of human intensive care patients. J Clin Endocrinol Metab, 99, 4214–22. Boonen E, et al. (2014). Reduced nocturnal ACTH-driven cortisol secretion during critical illness. Am J Physiol Endocrinol Metab, 306, E883–92. Boonen E, Bornstein SR, Van den Berghe G (2015). New insights into the controversy of adrenal function during critical illness. Lancet Diabetes Endocrinol, 3, 805–15. Casaer MP, et al. (2011). Early versus late parenteral nutrition in critic- ally ill adults. N Engl J Med, 365, 506–17. Casaer MP, Van den Berghe G (2014). Nutrition in the acute phase of critical illness. N Engl J Med, 370, 1227–36. Finfer S, et al. (2009). Intensive versus conventional glucose control in critically ill patients. N Engl J Med, 360, 1283–97. Finfer S, et al. (2012). Hypoglycemia and risk of death in critically ill patients. N Engl J Med, 367, 1108–18. Fliers E, et al. (2015). Thyroid function in critically ill patients. Lancet Diabetes Endocrinol, 3, 816–25. Gielen M, et al. (2012). Effect of tight glucose control with insulin on the thyroid axis of critically ill children and its relation with out- come. J Clin Endocrinol Metab, 97, 3569–76. Kosiborod M, et al. (2009). Relationship between spontaneous and iat- rogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA, 301, 1556–64. Langouche L, et al. (2013). Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its rela- tion with outcome: a randomized, controlled clinical study. J Clin Endocrinol Metab, 98, 1006–13. Meersseman P, et al. (2015). Effect of early parenteral nutrition on the HPA axis and on treatment with corticosteroids in intensive care pa- tients. J Clin Endocrinol Metab, 100, 2613–20. Mesotten D, et al. (2012). Neurocognitive development of children 4 years after critical illness and treatment with tight glucose con- trol: a randomized controlled trial. JAMA, 308, 1641–50. Sprung CL, et al. (2008). Hydrocortisone therapy for patients with septic shock. N Engl J Med, 358, 111–24. Van den Berghe G (2014). Non-thyroidal illness in the ICU: a syn- drome with different faces. Thyroid, 24, 1456–65. Van den Berghe G, de Zegher F, Bouillon R (1998). Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab, 83, 1827–34. Van den Berghe G, et al. (2001). Intensive insulin therapy in critically ill patients. N Engl J Med, 345, 1359–67. Van den Berghe G, et al. (2006). Intensive insulin therapy in the med- ical ICU. N Engl J Med, 354, 449–61. Vanhorebeek I, et al. (2006). Cortisol response to critical illness: effect of intensive insulin therapy. J Clin Endocrinol Metab, 91, 3803–13. Vlasselaers D, et al. (2009). Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet, 373, 547–56. Days Cumulative risk in-hospital mortality Expected outcomes for ranges of blood glucose based on Belgian trials .3 .2 .1 0 0 100 200 300 400 500 600 Blood glucose >150 mg/dl (>8.4 mmol/litre) Blood glucose 110–150 mg/dl (6.2–8.4 mmol/litre) Blood glucose <110 mg/dl (<6.2 mmol/litre) Fig. 17.9.6 The dose response for blood glucose ranges versus mortality is shown for the aggregated adult studies in Leuven. Reproduced from G. Van den Berghe (2012). Intensive insulin therapy in the ICU–reconciling the evidence. Nat Rev Endocrinol., 8, 374–378, with permission.

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