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Endocrine evaluation of patients with critical illness

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Critical illness is any condition requiring support of failing vital organ systems without which survival would not be possible. This life-threatening condition, which may be evoked by trauma, extensive surgery or severe medical illnesses, is an ultimate example of acute, severe physical stress. If onset of recovery does not follow within a few days of intensive care, critical illness often becomes prolonged and vital organ support is frequently needed for weeks. Feeding does not reverse ongoing wasting of protein from skeletal muscle and solid organs, which causes impairment of vital functions, weakness, and delayed or hampered recovery [1,2]. This is a frustrating clinical problem because despite adequate and successful treatment of the underlying disease, dependency on intensive care persists and susceptibility for potentially lethal (septic) complications increases. Indeed, mortality from prolonged critical illness is high: almost 3 out of 10 adult patients with an intensive care stay of more than three weeks do not survive [3]. Male patients seem to have a higher risk for adverse outcome of prolonged critical illness than female patients do, an observation, which remains unexplained [3]. In line with the foregoing is the inability of the classical scoring systems for severity of illness, such as APACHE II [4], to predict mortality in an individual chronic critically ill patient. This enigma reflects lack of understanding of the pathophysiologic mechanisms underlying onset of recovery or, conversely, the failure to recover from prolonged critically illness.

The acute and chronic phases of critical illness are associated with distinct endocrine alterations [5,6]. It remains a matter of debate whether or to what extent these changes are adaptive or contributing to the metabolic

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disturbances present in the critically ill. The endocrine stress responses are partially central and partially peripheral in origin. In addition, patients may have pre-existing central or peripheral endocrine diseases, either previously diagnosed or unknown. Hence, the puzzle is complex and endocrine function testing in a critically ill patient a major challenge. Furthermore, the inability to define the endocrine changes as either adaptation or pathology renders the issue of treatment even more controversial.

This article reviews the novel insights in the dynamic neuroendocrine alterations as they occur during the course of critical illness. It also highlights the complexity of differential diagnosis with pre-existing endocrine diseases and the available evidence of benefit or harm of certain endocrine interventions.

Somatotropic axis

In normal physiology, growth hormone (GH) is released from the pituitary somatotropes in a pulsatile fashion, under the interactive control of the hypothalamic GH-releasing hormone (GHRH), which is stimulatory, and somatostatin, which exerts an inhibitory effect [7]. Since the 1980s, a series of synthetic GH-releasing peptides (GHRPs) and nonpeptide analogs have been developed with potent GH-releasing capacities acting through a specific G-protein coupled receptor located in the hypothalamus and the pituitary [8,9]. The conserved endogenous ligand for this receptor has recently been discovered and named "ghrelin" [10]. Ghrelin originates in peripheral tissues, such as the stomach and in the hypothalamic arcuate nucleus, and there seems to be a third key factor in the complex physiologic regulation of pulsatile GH secretion. As shown in rodents [11], there is now evidence that in the humans [12], the pulsatile nature of GH secretion is important for its metabolic effects [3,13].

Alterations within the somatotropic axis in the acute phase of critical illness

During the first hours or days after an acute insult, such as surgery, trauma or infection, circulating GH levels become elevated and the normal GH profile, consisting of peaks alternating with virtually undetectable troughs, is altered: peak GH and interpulse concentrations are high and the GH pulse frequency is elevated (Fig. 1) [5,14,15]. It is still unclear which factor ultimately controls the stimulation of GH release in response to stress. As in starvation [16], more frequent withdrawal of the inhibitory somatostatin or an increased availability of stimulatory (hypothalamic or peripheral) GH-releasing factors could hypothetically be involved. Serum concentrations of insulin-like growth factor-1 (IGF-1) and the GH-dependent binding protein, IGF-binding protein-3 (IGFBP-3) and its acid-labile subunit (ALS) decrease, which is preceded by a drop in serum levels of GH-binding protein (GHBP) [17]. The latter was found to reflect reduced

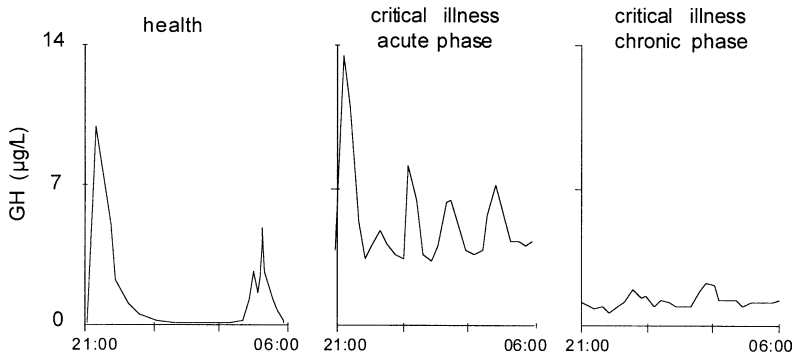

Fig. 1. Nocturnal serum concentration profiles of GH illustrating the differences between the acute phase and the chronic phase of critical illness within an intensive care setting. (*Adapted from* Van den Berghe G, de Zegher F, Bouillon R. Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 1998;83:1827–34; with permission.)

GH-receptor expression in peripheral tissues [17]. Circulating levels of the small IGF-binding proteins, such as IGFBP-1, IGFBP-2 and IGFBP-6 are elevated [18,19]. This constellation, which has been confirmed in experimental human and animal models of acute stress and in acutely ill patients, has been interpreted as acquired peripheral resistance to GH [14,18]. It has been suggested that these changes are brought about by the effects of cytokines, such as tumor necrosis factor-α (TNFα), interleukin 1 (IL-1), and IL-6, the hypothesis being that reduced GH receptor expression and thus low IGF-1 levels are the primary events (cytokine-induced) which, in turn, through reduced negative feedback inhibition, induces the abundant release of GH during acute stress, exerting direct lipolytic, insulin antagonizing and immune-stimulating actions, while the indirect IGF-1 mediated effects of GH are attenuated [20,21]. This explanation is plausible in that such changes would prioritize essential substrates, such as glucose, FFA and amino acids (glutamine) toward survival rather than anabolism. Increased IGFBP-3 protease activity in plasma has also been reported, however, and is believed to result in increased dissociation of IGF-1 from the ternary complex, thereby shortening the IGF-1 half-life in the circulation. The latter could theoretically be an adaptive escape mechanism to secure availability of free IGF-1 at the tissue level [22].

Distinct alterations within the somatotropic axis during chronic critical illness

In chronic critical illness, the changes observed within the somatotropic axis are different. First, the pattern of GH secretion is chaotic and the amount of GH, which is released in pulses, is reduced compared with the acute phase (Fig. 1) [6,23–25]. Moreover, although the nonpulsatile fraction

is still somewhat elevated and the number of pulses is still high, mean nocturnal GH serum concentrations are scarcely elevated, if at all [23], when compared with the healthy, nonstressed condition, and substantially lower than in the acute phase of stress [5]. The authors observed that, when intensive care patients are studied from 7 to 10 days illness onward, in the absence of drugs known to exert profound effects on GH secretion such as dopamine [26,27] and calcium channel blockers or glucocorticoids, mean nocturnal GH levels are uniformly around 1 μg/L [23], trough levels are easily detectable (and thus still elevated) and peak GH levels hardly ever exceed 2 μg/L [6,23–25]. These results are surprisingly independent of the patient's age, gender, body composition and type of underlying disease [3,5]. Second, only the pulsatile fraction of GH secretion—which is substantially reduced—correlates positively with circulating levels of IGF-1, IGFBP-3, and ALS, all of which are low [6,24,25]. Thus the more pulsatile GH secretion is suppressed, the lower the circulating levels of the GH dependent IGF-1 and ternary complex binding proteins become, and this no longer represents a state of GH resistance. Elevated serum levels of GHBP [3], assumed to reflect GH receptor expression in peripheral tissues, in prolonged critically ill patients compared with those measured in a matched control group are in line with recovery of GH responsiveness with time during severe illness [3,6]. Moreover, low serum levels of GH-dependent IGF-1 and binding proteins (IGFBP-3, ALS, and IGFBP-5) are tightly related to biochemical markers of impaired anabolism such as low serum osteocalcin and leptin concentrations during prolonged critical illness [6]. These findings suggest that relative GH deficiency, epitomized by reduced pulsatile GH secretion, participates in the pathogenesis of the "wasting syndrome" especially in the chronic phase of critical illness. Furthermore there is a gender dissociation in that men show a greater loss of pulsatility and regularity within the GH secretory pattern than women (despite indistinguishable total GH output) and concomitantly lower IGF-1 and ALS levels (Fig. 2) [3]. It remains unknown if the (paradoxical) sexual dimorphism within the GH/IGF-1 axis and the fact that men seem to be at higher risk for an adverse outcome from chronic critical illness than women [3] is a casual or causal association.

Pathophysiology of chronic changes within the somatotropic axis

The pathogenesis of the secretory pattern of GH in prolonged critical illness is probably complex. One of the possibilities is that the pituitary is taking part in the "multiple organ failure syndrome" becoming unable to synthesize and secrete GH. An alternative explanation could be that the lack of pulsatile GH secretion is due to increased somatostatin tone or to a reduced stimulation by endogenous releasing factors, such as GHRH or ghrelin. Studying GH responses to administration of GH-secretagogues (GHRH and GHRP), in a saturating dose, enables to differentiate between

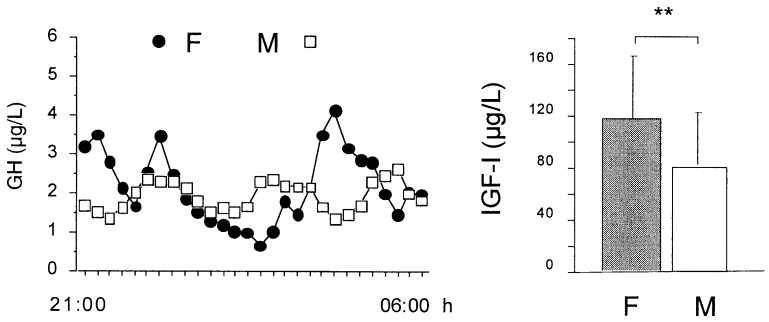

Fig. 2. The more "feminized" pattern of GH secretion (more irregular and less pulsatile GH secretory pattern for an identical mean nocturnal GH level) in prolonged critically ill men compared with women is illustrated by the representative nocturnal (21:00h–06:00h) GH serum concentration series (sampling every 20 minutes) obtained in a male (*squares*) and a matched female (*circles*) patient. Concomitantly, protracted critically ill men have lower circulating levels of IGF-1 than women do. IGF-1 results are presented as mean ± SD. ** $P < 0.01$. (*Adapted from* Van den Berghe G, Baxter RC, Weekers F, et al. A paradoxical gender dissociation within the GH insulin-like growth factor I axis during protracted critical illness. J Clin Endocrinol Metab 2000;85:183–92; with permission.)

a primarily pituitary and a hypothalamic origin of the impaired GH release in prolonged critically ill patients. Indeed, the combined administration of GHRH and GHRP seems to be a most powerful stimulus for pituitary GH release in humans [28]. A low GH response in critical illness would thus fit with a pituitary dysfunction or a high somatostatin tone and a high GH response would be compatible with reduced (hypothalamic) stimulation of the somatotropes.

We found that GH responses to a bolus injection of GHRP are high in prolonged critically ill patients and several-fold higher than the response to GHRH, the latter being normal or often subnormal [29]. GHRH + GHRP evokes a clear synergistic response in this condition, revealing the highest GH responses ever reported in a human study [29]. The high GH responses to secretagogues exclude the possibility that the blunted GH secretion during protracted critical illness is due to a lack of pituitary capacity to synthesize GH or is due to accentuated somatostatin-induced suppression of GH release. Inferentially, one of the mechanisms that could be involved is reduced availability of ghrelin. Ultimately, the combination of low availability of somatostatin and of an endogenous GHRP-like ligand, such as ghrelin emerges as a plausible mechanism that clarifies (1) the reduced GH burst amplitude, (2) the increased frequency of spontaneous GH secretory bursts, (3) the elevated interpulse levels, and (4) the striking responsiveness to GHRP alone or in combination with GHRH and this without markedly increased responsiveness to GHRH alone. Female patients with prolonged critical illness have a markedly higher response to a bolus of GHRP compared with male patients, a difference, which is annihilated at the time GHRH is injected together with GHRP (Fig. 3) [3]. Less endogenous GHRH

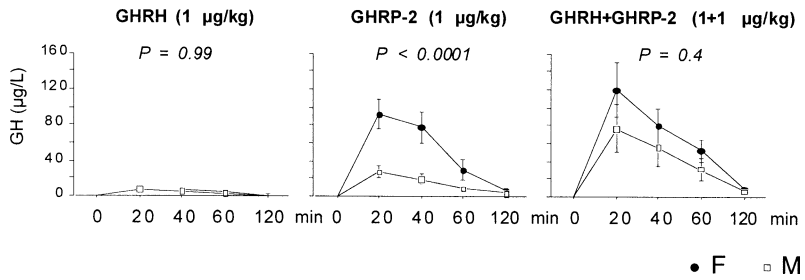

Fig. 3. Responses (increments above baseline) of GH obtained 20, 40, 60, and 120 minutes after intravenous bolus administration of GHRH (1 µg/kg), GHRP-2 (1 µg/kg), and GHRH + GHRP-2 (1 + 1 µg/kg) in matched male and female protracted critically ill patients. Five men and 5 women were randomly allocated to each secretagogue group. Results are presented as mean ± SEM. Circles depict results from female and squares from male patients. *P* values were obtained using repeated measures ANOVA. (*Adapted from* Van den Berghe G, Baxter RC, Weekers F, et al. A paradoxical gender dissociation within the GH insulin-like growth factor I axis during protracted critical illness. J Clin Endocrinol Metab 2000;85:183–92; with permission.)

action in prolonged critically ill men, possibly due to the concomitant profound hypoandrogenism [3], accompanying loss of action of an endogenous GHRP-like ligand with prolonged stress in both genders, may explain this finding.

Effects of GH-releasing factors in the chronic phase of critical illness

The hypothesis of reduced endogenous stimulation of GH secretion in prolonged critical illness was further explored by examining the effects of continuous infusion of GHRP +/− GHRH. Continuously infusing GHRP (1 µg/kg/h), and even more so GHRH + GHRP (1 + 1 µg/kg/h), for up to 2 days was found to substantially amplify pulsatile GH secretion (> 6-fold and > 10-fold respectively) in this condition, without altering the high burst frequency (Fig. 4) [24,25]. Reactivating pulsatile GH secretion evoked a proportionate increase in serum IGF-1 (66% and 106%), IGFBP-3 (50% and 56%) and ALS (65% and 97%), indicating peripheral GH-responsiveness (Fig. 4) [24,25]. The presence of considerable responsiveness to reactivated pulsatile GH secretion in these patients and the high serum levels of GHBP clearly delineates the distinct pathophysiologic paradigm present in the chronic phase of critical illness as opposed to the acute phase, which is believed to be primarily a condition of GH-resistance. After 2 days treatment with GHRP, (near) normal levels of IGF-1, IGFBP-3, IGFBP-5, and ALS are reached and, as shown in a subsequent study, maintained for at least 5 days (Fig. 5) [6]. GH secretion after 5 days treatment with GH-secretagogues was found to be lower than after 2 days, suggesting active feedback inhibition loops, which most likely prevented overtreatment [6,25]. In this study, where GHRP was infused together with TRH for 5 days, the self-limiting endocrine responses induced anabolism at the level of several

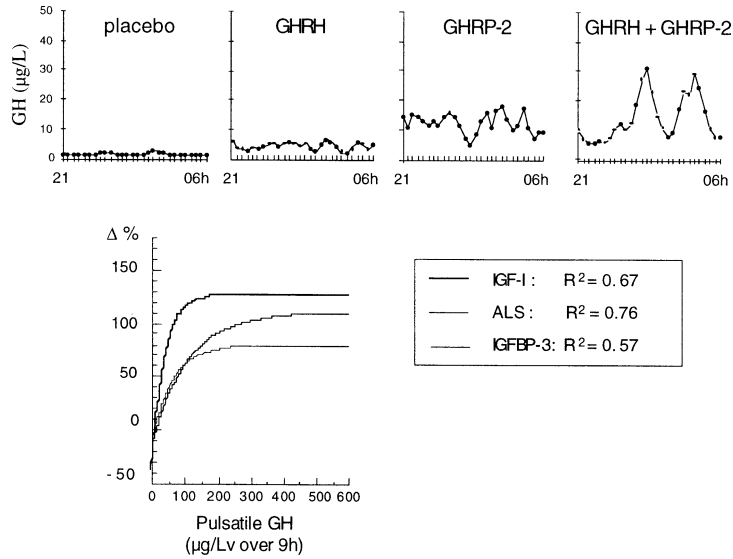

Fig. 4. Nocturnal serum GH profiles in the prolonged phase of illness illustrating the effects of continuous infusion of placebo, GHRH (1 µg/kg/h), GHRP-2 (1 µg/kg/h), or GHRH + GHRP-2 (1 + 1 µg/kg/h). Exponential regression lines have been reported between pulsatile GH secretion and the changes in circulating IGF-1, ALS, and IGFBP-3 obtained with 45-hour infusion of either placebo, GHRP-2 or GHRH + GHRP-2. They indicate that the parameters of GH responsiveness increase in proportion to GH secretion up to a certain point, beyond which further increase of GH secretion has apparently little or no additional effect. It is noteworthy that the latter point corresponds to a pulsatile GH secretion of approximately 200 µg/Lv over 9 hours, or less, a value that can usually be evoked by the infusion of GHRP-2 alone. In chronic critical illness, GH-sensitivity is clearly present, in contrast to the acute phase of illness, which is believed to be primarily a condition of GH resistance. (*Adapted from* Van den Berghe G, de Zegher F, Bouillon R. Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 1998;83:1827–34; with permission.)

peripheral tissues, as indicated by an increase in serum levels of osteocalcin, insulin, and leptin and a decrease in urea production [6]. Usually, infusion of GHRP without GHRH suffices to reactivate pulsatile GH secretion and to elicit the IGF-1 and IGFBP responses in prolonged critical illness. In critically ill men, in particular those with a long intensive care stay, it may be necessary to add a low dose of GHRH (0.1 µg/kg/h suffices) (G. Van den Berghe, unpublished observations) because of the simultaneous lack of endogenous GHRH activity accompanying the reduced availability of the GHRP-like ligand.

Treatment with GH during critical illness

In view of the anabolic properties of GH and IGF-1, a large multicenter study investigated the effects of high dose GH treatment in long-stay intensive care patients [30]. Instead of improving outcome, this intervention

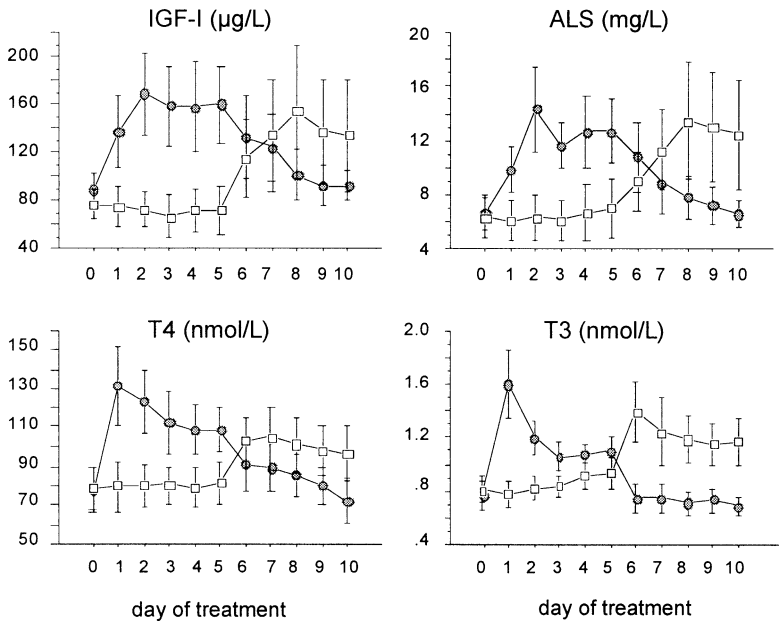

Fig. 5. Serum concentrations (mean ± SEM) of IGF-1, ALS, T4 and T3 in response to a randomized treatment with either 5 days GHRP-2 + TRH infusion (1 + 1 µg/kg/h) followed by 5 days placebo (*circles*) or 5 days placebo followed by 5 days GHRP-2 + TRH infusion (1 + 1 µg/kg/h) (*squares*) in a group of 10 male and 4 female critically ill ventilated ICU patients. All $P < 0.0001$ with ANOVA. The mean age of the patients was 68 years. The mean intensive care stay at the time of study start was 40 days. (*Adapted from* Van den Berghe G, Wouters P, Weekers F, et al. Reactivation of pituitary hormone releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab 1999;84:1311–23; with permission.)

doubled mortality and worsened morbidity. Although the authors of this study did not provide an explanation for the unexpected outcome, the difference between the acute and chronic stress response may be important. The rationale for the use of high GH doses in that trial has presumably been the extrapolation, now invalidated, that all conditions of stress-associated hypercatabolism, and thus also the catabolic state of prolonged critical illness, are brought about by resistance to GH in the presence of normal or adaptively altered pituitary function, and that the induction of anabolism in these conditions would thus require high GH doses. The knowledge that is now available on the different states of the somatotropic axis in acute and prolonged critical illness clarifies, at least partially, why the administration of high GH doses to sick, but often GH-responsive patients may have evoked side effects. Indeed, high doses of GH administered in the chronic phase of critical illness can induce IGF-1 levels into the acromegalic range, excessive fluid retention (up to 20% of body weight), hypercalcemia, and pronounced insulin resistance with hyperglycemia [31]. In view of the broad

spectrum of target tissues for GH, and taking into account the pre-existing impairment of vital organ functions in the critically ill, the excessive doses of GH may have further deteriorated the function of multiple organs.

A question that arises from the results of this trial is what intensive care physicians should do at the time patients, who are GH deficient and are on GH treatment, become critically ill and admitted to the ICU. Should GH substitution therapy be discontinued at that occasion? A consensus statement from the GH-Research Society [32] advises not to discontinue in view of the lack of evidence that the low GH doses used for substitution therapy are harmful.

Thyrotropic axis

Changes in the acute phase of critical illness

Within 2 hours after surgery or trauma, serum levels of T3 decrease whereas T4 and TSH briefly increase (Fig. 6) [33]. Apparently, low T3 levels at that stage are mainly caused by a decreased peripheral conversion of T4 to T3 [34]. Subsequently, circulating TSH and T4 levels often return to "normal" whereas T3 levels remain low. Although mean serum TSH concentrations are indistinguishable from normal at that point, the normal

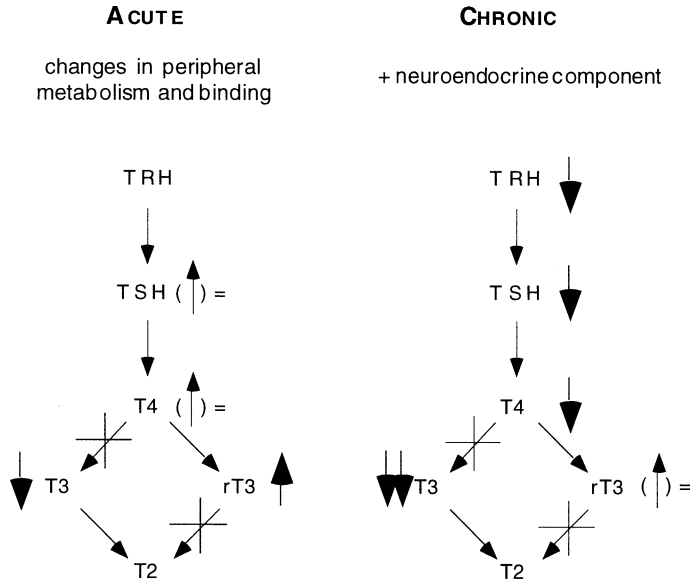

Fig. 6. Simplified overview of the major changes occurring within the thyroid axis during the acute and the chronic phase of critical illness. (*Adapted from* Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1–13; with permission).

nocturnal TSH surge is absent [35,36]. The magnitude of the T3 drop within 24 hours has been found to reflect the severity of illness [37,38]. The cytokines TNFα, IL-1, and IL-6 have been investigated as putative mediators of the acute low T3 syndrome. Although these cytokines are capable of mimicking the acute stress-induced alterations in thyroid status, cytokine antagonism in a human model failed to restore normal thyroid function [39]. Low concentrations of binding proteins and inhibition of hormone binding, transport and metabolism by elevated levels of free fatty acids, and bilirubin have been proposed as factors contributing to the low T3 syndrome at tissue level [40]. Teleologically, the acute changes in the thyroid axis may reflect an attempt to reduce energy expenditure, as happens during starvation [41], and thus as an appropriate response that does not warrant intervention. This, however, remains a controversial issue because valid data to support or refute this statement are lacking [42]. Although short-term intravenous administration of T3 to patients after cross clamp removal during elective coronary bypass grafting has shown to improve postoperative cardiac function [43,44], the pharmacologic doses of T3 that resulted in supranormal serum T3 levels and the absence of an effect on mortality do not refute an adaptive nature of the "acute" low T3 syndrome.

Changes in prolonged critical illness

Patients treated in intensive care units for several weeks present with a somewhat different set of changes within the thyroid axis. A single sample usually reveals low or low-normal TSH values and low T4 and T3 serum concentrations [45]. Overnight repeated sampling, however, revealed that essentially the pulsatility in the TSH secretory pattern is dramatically diminished and that, as for the GH axis, it is the loss of TSH pulse amplitude which is related to low serum levels of thyroid hormone [45]. Moreover, Fliers and coworkers have elegantly demonstrated by post-mortem examination of human brain specimen that at the time death follows chronic severe illness, the expression of TRH gene in hypothalamic paraventricular nuclei is reduced whereas this is not the case after death from acute insults such as lethal trauma due to a road accident [46]. These researchers observed a positive correlation between TRH mRNA in the paraventricular nuclei and blood levels of TSH and T3. Together, these findings indicate that production and or release of thyroid hormones is reduced in the chronic phase of critical illness, due to reduced hypothalamic stimulation of the thyrotropes, in turn leading to reduced stimulation of the thyroid gland. In line with this concept is the increase of TSH marking onset of recovery from severe illness [47]. The exact mechanisms underlying the neuroendocrine pathogenesis of the low thyroid hormone levels in prolonged critical illness are unknown. As circulating cytokine levels are usually much lower at that stage [48], other mechanisms operational within the central nervous system are presumably involved. Endogenous dopamine and prolonged

hypercortisolism may each play a role because exogenous dopamine and glucocorticoids are known to provoke or aggravate hypothyroidism in critical illness [49,50].

Low thyroid hormone levels in protracted critical illness correlate inversely with urea production and bone degradation which could reflect either an adaptive, protective mechanism against hypercatabolism or a causal relation [6]. Restoring physiologic levels of thyroid hormones by continuously infusing TRH (together with a GH-secretagogue) (Fig. 5) was found to reduce rather than increase hypercatabolism [6], an effect that was related only to thyroid hormone changes. During TRH infusion in prolonged critical illness, the negative feedback exerted by thyroid hormones on the thyrotropes was found to be maintained, thus precluding overstimulation of the thyroid axis [23,25]. This self-limitation may be extremely important during critical illness to avoid hyperthyroidism, which would inadvertently aggravate catabolism. The coinfusion of TRH and GH-releasing factors seems a better strategy than the infusion of TRH alone because the combination, but not TRH alone, avoids an increase in circulating reverse T3 [6,23]. The latter may point to the effect of GH on the activity of type I deiodinase and eventually to other important interactions among different anterior pituitary axes for optimal peripheral responses [51].

Treatment with thyroid hormone or releasing factors during prolonged critical illness

It remains controversial whether correction of the illness-associated low serum and tissue concentrations of T3 by either T4 or T3 administration is required to improve clinical problems distinctively associated with prolonged critical illness [52,53]. Pioneering studies with T4 administration so far have failed to demonstrate clinical benefit within an intensive care setting, but in view of the impaired conversion of T4 to T3, this is not really surprising [54,55]. A recent report on thyroid hormone treatment using substitution doses of T3 in dopamine-treated pediatric patients after correction of congenital anomaly revealed improvement of postoperative cardiac function [56]. In contrast to treatment with thyroid hormones, infusing TRH allows for peripheral shifts in thyroid hormone metabolism during intercurrent events and, accordingly, permits the body to elaborate appropriate concentrations of thyroid hormones in the circulation and at tissue level, thus setting the scene for a safer treatment than the administration of T3 [25]. The peripheral tissue responses to the normalization of serum concentrations of IGF-1 and binding proteins as evoked by GHRP infusion seem to depend on the coinfusion of TRH and the concomitant normalization of the thyroid axis. Indeed, GHRP-2 infused alone evokes identical increments in serum concentrations of IGF-1, IGFBP-3, and ALS, but is devoid of the anabolic tissue responses that are present with the combined infusion of GHRP and

TRH [23]. Outcome benefit of TRH infusion alone or in combination with GH-secretagogues in prolonged critical illness is yet to be studied.

The diagnosis of pre-existing thyroid disease and its management during critical illness can be extremely difficult and in view of the controversy, recommendations for clinical practice is often not evidence-based. In view of the hypothalamic-pituitary suppression occurring in the chronic phase of critical illness in patients without previous endocrine disease, it is virtually impossible to diagnose pre-existing central hypothyroidism during the time a patient is treated within the ICU. Patients with pre-existing primary hypothyroidism, myxedema coma being the extreme presentation, are expected to show low serum levels of T4 and T3 in combination with high TSH concentrations. A complicating factor, however, is the simultaneous presence of primary hypothyroidism and severe nonthyroidal critical illness. Indeed, the nonthyroidal critical illness evokes the sum of changes within the hypothalamus–pituitary–thyroid axis occurring in the framework of disease, as described earlier. A decrease in serum T3 and an increase in serum reverse T3 (rT3) are the most common changes in acute nonthyroidal critical illness, but serum T3 may be undetectable and serum T4 also dramatically reduced in patients with protracted nonthyroidal critical illness. Therefore, in patients with myxedema coma with severe comorbidity (pneumonia, sepsis) serum T3 and T4 will be low, but could be indistinguishable from those values observed in prolonged nonthyroidal critical illness. Whereas serum TSH is markedly increased in uncomplicated primary hypothyroidism, it is paradoxically normal or even decreased in severely ill patients. Therefore, serum TSH may be lower than anticipated, from the severe hypothyroid condition of the patient with myxedema coma and concomitant illness, or even frankly low. Thus, a high serum TSH concentration, when observed, is in agreement with primary hypothyroidism but a normal or a low TSH does not exclude it during intercurrent critical illness. Indeed, serum TSH may be paradoxically low in this setting because of concomitant nonthyroidal critical illness, especially in patients given high-dose corticosteroids or dopamine. Other iatrogenic factors causing hypothyroidism, particularly in a surgical ICU, are iodine wound dressings, iodine containing contrast agents used for radiologic imaging, and drugs such as somatostatin and amiodarone. The finding of a high ratio of T3 to T4 in serum, a low thyroid hormone-binding ratio, and a low serum rT3 may favor the presence of primary hypothyroidism, whereas opposite changes occur in nonthyroidal critical illness. The diagnostic accuracy of any of these measurements is limited and in many patients no definite laboratory diagnosis can be established. In these patients, history, physical examination, and the possible presence of thyroid autoantibodies may give further clues to the presence or absence of thyroid disease. Repeated thyroid function tests after improvement of the nonthyroidal illness will provide a final answer.

When and how to treat primary hypothyroidism during the course of an intercurrent nonthyroidal critical illness remains controversial. One

exception, however, is a presumed diagnosis of myxedema coma, for which there is general agreement that patients should be treated with a parenteral form of thyroid hormone. The proper initiation of thyroid hormone replacement therapy, however, in this case, still remains controversial because controlled studies on the optimal treatment regimen are lacking. The first uncertainty relates to the type of thyroid hormone to be given: should it be T4 alone, T3 alone or the combination of both. The second uncertainty is the optimal initial dosage of any thyroid hormone replacement regimen. Many clinicians prefer a loading dose of up to 300 to 500 μg intravenous T4 to quickly restore circulating levels of T4 to approximately 50% of the euthyroid value [57,58], followed by 50 to 100 μg of intravenous T4 daily until oral medication can be given. Higher doses do not seem to be beneficial, although Kaptein et al [59] found no increased cardiovascular risk in severely ill hypothyroid patients treated with larger doses of T4.

Some authors have advocated the use of T3 in addition to T4 because T3 does not require conversion by 5′-deiodinase enzymes to a biologically active form. In an animal experimental study by Morreale de Escobar et al [60] replacement therapy for hypothyroidism with T4 alone did not ensure euthyroidism in all tissues, and a subsequent study showed that only the combined treatment with T4 and T3 induces euthyroidism in all tissues. Tissue-specific deiodinase activities acting as local regulatory mechanisms are the presumed explanation for these findings. In a recent study in hypothyroid patients it appeared that partial substitution of T3 for T4 might improve mood and neuropsychologic function in hypothyroid patients, possibly by increased bioavailability of T3 in the CNS [61]. Whereas these fascinating results await confirmation by others, replacement therapy with a combination of T4 and T3 in compensated hypothyroidism remains an experimental modality [62].

The author's experimental protocol for thyroid hormone therapy during intensive care of presumed hypothyroidism, either pre-existing or iatrogenically induced at the time reversal of the iatrogenic cause seems impossible, advises a dose of 100 to 200 μg T4 IV bolus per 24h combined with T3 0.6 μg/kg ideal body weight per 24h in continuous IV infusion, targeting thyroid hormone levels in the low normal range (G. Van den Berghe et al, unpublished data, 2002).

Lactotropic axis

Prolactin responses to acute and prolonged critical illness

It has been suggested that the changes in prolactin secretion in response to stress may contribute to altered immune function during the course of critical illness. The evidence for this includes the presence of prolactin receptors on human T- and B-lymphocytes [63] and the prolactin dependency of T-lymphocytes for maintaining immune competence [64].

In mice, inhibition of prolactin release results in impaired lymphocyte function, in depressed lymphokine-dependent macrophage activation, and in death from a normally nonlethal exposure to bacteria [65]. The immune suppressive drug, Cyclosporine, is known to compete with prolactin for a common binding site on T-cells which may explain part of its effects [66,67]. The prolactin-suppressing drug, bromocriptine, has been shown to be an adjuvant immunosuppressant in humans after heart transplantation [67]. Prolactin was among the first hormones known to have increased serum concentrations in response to acute physical or psychologic stress [68], an increase that may be mediated by VIP, oxytocin, dopaminergic pathways or other still uncharacterized factors. Cytokines may again play a signaling role. Whether hyperprolactinemia during the initial phase of critical illness contributes to the vital initial activation of the immune cascade remains speculative.

In chronic critical illness, serum prolactin levels are no longer as high as in the acute phase and the secretory pattern is characterized by a reduced pulsatile fraction [25,41]. A role for endogenous dopamine has been suggested [69]. It is unknown whether the blunted prolactin secretion in the chronic phase plays a role in the anergic immune dysfunction or in the increased susceptibility for infections characterizing the chronically ill [70]. Exogenous dopamine, often infused as an inotropic drug in intensive care-dependent patients, has been shown to further suppress prolactin secretion and was found to aggravate concomitantly T-lymphocyte dysfunction and impaired neutrophyl chemotaxis [69,71].

Prolactin as a therapeutic target?

Prolactin is currently not available for therapy. Future studies are needed to evaluate the therapeutic potential of thyrotropin releasing hormone-induced prolactin release for optimizing immune function during critical illness [50]. Also, it remains enigmatic whether patients on treatment for prolactinoma should interrupt or continue this treatment during an intercurrent critical illness.

Luteinizing hormone–testosterone axis

Changes in LH–testosterone axis in acute and prolonged critical illness

Also for LH, the pulsatility in the secretory pattern is important for its bioactivity [72,73]. Because testosterone is the most important endogenous anabolic steroid, changes within the LH–testosterone axis in the male could be relevant for the catabolic state of critical illness. Low serum testosterone levels in men accompany a variety of catabolic states. These conditions include starvation [74,75], the postoperative phase [76], myocardial

infarction [77], burn injury [78,79], psychologic and physical stress [80,81], and chronic critical illness [82].

Low serum testosterone concentrations and elevated LH levels observed during the acute stress of surgery or myocardial infarction [76,77,83] suggest an immediate Leydig-cell suppression, of which the exact cause remains obscure. Inflammatory cytokines (IL-1 and IL-2) may play a role, as suggested by experimental studies [84,85]. It may be considered as appropriate that the secretion of anabolic androgens be switched off in circumstances of acute stress, to conserve energy and metabolic substrates for, at that time at least, less vital functions.

When critical illness becomes prolonged, hypogonadotropism develops [78,86]. Concomitantly, circulating levels of testosterone become extremely low (often undetectable) in men whereas estimated free estradiol concentrations remain normal suggesting increased aromatization of adrenal androgens [3]. The progressive decrease of serum gonadotropin levels, however, seems to lag behind the rapid decline in serum testosterone [77,83,87]. In prolonged critically ill men, a high LH pulse frequency with an abnormally low LH pulse amplitude has been observed [82], which was interpreted as an impaired compensatory LH hypersecretion in response to the low serum testosterone levels. Thus, again, it seems to be mainly an impairment of the pulsatile component of LH secretion, which occurs in response to the sustained stress of prolonged critical illness [82]. Endogenous dopamine, opiates and the preserved estradiol levels [3] may be involved in the pathogenesis of hypogonadotropism, as exogenous dopamine, opioids, and estrogens may further diminish blunted LH secretion [82,88].

Animal data suggest that prolonged exposure of the brain to IL-1 may also play a role through the suppression of LHRH synthesis [84]. The pioneering studies evaluating androgen treatment in prolonged critical illness failed to demonstrate conclusive clinical benefit [89]. In view of the secretory characteristics of the other anterior pituitary hormones, we recently investigated the therapeutic potential of LHRH pulses in prolonged critically ill men, alone and together with GHRP-2 and TRH. LHRH alone seems only partially and transiently effective [90]. When LHRH pulses were given together with GHRP-2 and TRH infusion however, target organ responses and anabolic effects followed [23]. These data underline the importance of correcting all the hypothalamic/pituitary defects instead of applying a single hormone treatment.

Sex steroid substitution therapy during critical illness?

Because critical illness in itself induces profound hypoandrogenism in male patients, of which it remains unknown whether this reflects adaptation or pathology, it is not clear if androgen substitution therapy for pre-existing hypogonadism should be interrupted or continued during the course of an intercurrent critical illness. Sex steroids in women are usually not continued during critical illness.

Pituitary–adrenal axis

Pituitary–adrenal responses to acute and prolonged critical illness

The pituitary–adrenal axis also responds differently to acute and prolonged critical illness. It has been long known that the vital stress-induced hypercortisolism induced by surgery, trauma or sepsis, is associated with augmented ACTH release, which, in turn, is presumably driven by corticotrophin-releasing hormone (CRH), cytokines and the noradrenergic system. Concomitantly, circulating aldosterone increases markedly, most likely under the control of an activated renin-angiotensin system [91]. Hypercortisolism acutely shifts carbohydrate, fat, and protein metabolism, so that energy is instantly and selectively available to vital organs such as the brain and anabolism is delayed. Intravascular fluid retention and the enhanced inotropic and vasopressor response to respectively catecholamines and angiotensin II offer hemodynamic advantages in the "fight and flight" response. In addition, hypercortisolism elicited by acute disease or trauma can be interpreted as an attempt of the organism to mute its own inflammatory cascade, thus protecting itself against overresponses [92–94].

In chronic critical illness, serum ACTH was found to be low while cortisol concentrations remained elevated, indicating that cortisol release may in this phase be driven through an alternative pathway, possibly involving endothelin [95]. Why ACTH levels are low in chronic critical illness is unclear; a role for atrial natriuretic peptide or substance P has been suggested [95]. In contrast to serum cortisol, circulating levels of adrenal androgens such as dehydroepiandrosterone sulfate (DHEAS), which has immunostimulatory properties on Th1–helper-cells, are low during chronic critical illness [96–98]. Moreover, despite increased plasma renin activity, paradoxically decreased concentrations of aldosterone are found in protracted critical illness [99]. This constellation suggests a shift of pregnenolone metabolism away from mineralocorticoid and adrenal androgen pathways toward the glucocorticoid pathway, orchestrated by an unknown peripheral drive. Ultimately, the latter mechanism may also fail, as indicated by a 20-fold higher incidence of adrenal insufficiency present in critically ill patients over age 50 years and being treated at the intensive care unit for more than 14 days [100]. This type of relative adrenal failure coincides with adverse outcome and suggests that high levels of glucocorticoids remain essential for hemodynamic stability. Whether hypercortisolism in the chronic phase of critical illness is exclusively beneficial remains uncertain. Sustained hypercortisolism in the presence of low levels of DHEAS and prolactin could theoretically evoke imbalance between immunosuppressive and immunostimulatory pathways and thus could be seen as participating in the increased susceptibility for infectious complications. Other conceivable though unproven drawbacks of prolonged hypercortisolism include impaired wound healing and myopathy, complications that are often observed during protracted critical illness.

Treatment of adrenal failure during critical illness

In a patient with previously diagnosed primary or central adrenal insufficiency and in patients previously treated with systemic glucocorticoids, treatment should be continued and additional coverage for the stress of critical illness should be provided. For more details, we refer to previous chapters in this issue. Also, a true Addisonian crisis needs treatment in severe stress conditions. Hydrocortisone 100 mg followed by 50 to 100 mg every 6 hours on the first day, 50 mg every 6 hours on the second day, and 25 mg every 6 hours on the third day, tapering to a maintenance dose by the fourth to fifth day. In prolonged critical conditions, the maintenance dose should be kept two to three times the basal need. Special attention should be given to patients with concomitant diabetes insipidus, as lack of cortisol may prevent polyuria because cortisol is needed for free-water clearance. Inversely, in these patients glucocorticoid therapy may induce or aggravate diabetes insipidus. Another specific condition is the post-hypophysectomy-phase for Cushing's disease, characterized by a high vulnerability for Addisonian-like crisis. Drugs such as phenytoin, barbiturates, rifampicin and thyroid hormone can accelerate glucocorticoid metabolism by induction of microsomal enzyme activity and can increase the glucocorticoid replacement dose requirements. If this increased requirement is not met, adrenal crisis may occur.

Recently, however, the concept of relative hyopthalamic–pituitary–adrenal insufficiency in acute sepsis has been launched [101–103], which advocates short-term treatment with stress doses of glucocortioids as beneficial in patients without a full blown adrenal failure [104,105]. The controversy about this concept of relative adrenal axis failure in acute stress conditions is explained by the problems regarding diagnosis. Indeed, accurate ''normal'' values for baseline cortisol levels in this type of stress, normal reference values for cortisol responses to a short ACTH test, and data to support the option to use a low dose or high dose ACTH test [103,106], are still unavailable. Another issue of controversy regarding the concept of relative adrenal failure in acute sepsis is the dose and the duration of treatment once it has been initiated. Treating septic patients with glucocorticoids at too high a dose and for too long a time will conceivably aggravate the loss of lean tissue, prolong the ICU-dependency, and increase the susceptibility for potentially lethal complications.

Endocrine predictors of adverse outcome of critical illness

In the acute phase of critical illness, a high serum cortisol or low T3 concentrations [38], indicate poor prognosis. In the prolonged critically ill patient, however, these markers lack sensitivity. Recently, preliminary data were published showing that another parameter—serum concentration of

IGFBP-1—seems to predict outcome of chronic critical illness [3,6,107] (Fig. 7). IGFBP-1 is a small IGF binding protein produced almost exclusively in the liver (except in pregnancy). It is distinct among the members of the IGFBP family in it being acutely regulated by metabolic stimuli [108]. Studies with cultured human liver explants suggest that the major regulatory influences on IGFBP-1 production are insulin; which is inhibitory, and hepatic substrate deprivation; which is stimulatory, acting through a cyclic AMP-dependent mechanism [109,110]. Moreover, an inverse correlation of IGFBP-1 with IGF-1 and the GH-dependent proteins ALS and IGFBP-3 during critical illness is consistent with its inverse regulation by GH, as previously suggested [111–113].

The higher IGFBP-1 levels observed in prolonged critically ill patients who did not survive coincided with lower insulin concentrations compared with survivors, for the same range of blood glucose level—a surprising finding considering that these patients are believed to be insulin resistant (Fig. 7). Whether or not this also indicates that insulin secretion is becoming impaired in the long stay intensive care patients remains unclear. It is clear, however, that in unfavorable metabolic conditions, the hepatocyte alters its production of IGF-regulatory proteins, for which the trigger might be reduced hepatocyte substrate availability (theoretically caused by either hepatic hypoperfusion or hypoxia, hypoglycemia, and relative insulin deficiency or hepatic insulin resistance) leading to increased cyclic AMP production, which would suppress IGF-1 and ALS [114] and stimulate IGFBP-1 [110]. It is unclear to what extent loss of GH pulsatility may contribute to this switch, but recent data [6] suggest that activation of hepatic IGF-1 and ALS expression may require pulsatile GH, and animal studies similarly suggest that suppression of hepatic IGFBP-1 expression by insulin requires acute, rather than prolonged or nonpulsatile, GH action [115].

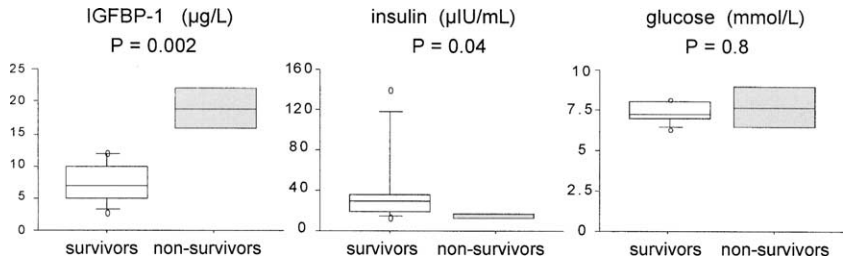

Fig. 7. Serum IGFBP-1 concentration is higher in nonsurvivors compared with survivors in prolonged critical illness. Concomitantly, nonsurvivors revealed lower serum insulin levels for the same blood glucose level. Box plots represent medians, P25–P75 and P10–P90 and circles represent the absolute values for outliers. (*Adapted from* Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1–13; with permission).

It remains unclear why long-stay intensive care patients fail to recover and eventually die, despite optimal intensive care. Further exploring the apparent link between serum IGFBP-1 levels, insulin, and outcome of prolonged critical illness will shed new light on the pathophysiologic processes crucial for recovery and survival. We recently showed that strict glycemic control below 110 mg/dL with intensive insulin therapy reduces morbidity and mortality of intensive care-dependent critical illness [116] (Fig. 8). Furthermore, as mentioned previously, the difference between the acute and chronic stress response may not be trivial in relation to outcome of critical illness. It was the (inappropriate) assumption that acute stress responses, such as GH resistance, persist throughout the course of critical illness, which had formed the (inappropriate) justification to administer high doses of GH to long-stay intensive care patients to induce anabolism [30]. The concomitant endocrine changes in chronic critical illness may have predisposed to severe side effects of high doses of GH. In view of the significant benefits of strict glycemic control using exogenous insulin recently demonstrated in ICU patients [116], GH-induced insulin resistance and hyperglycemia may have played a role.

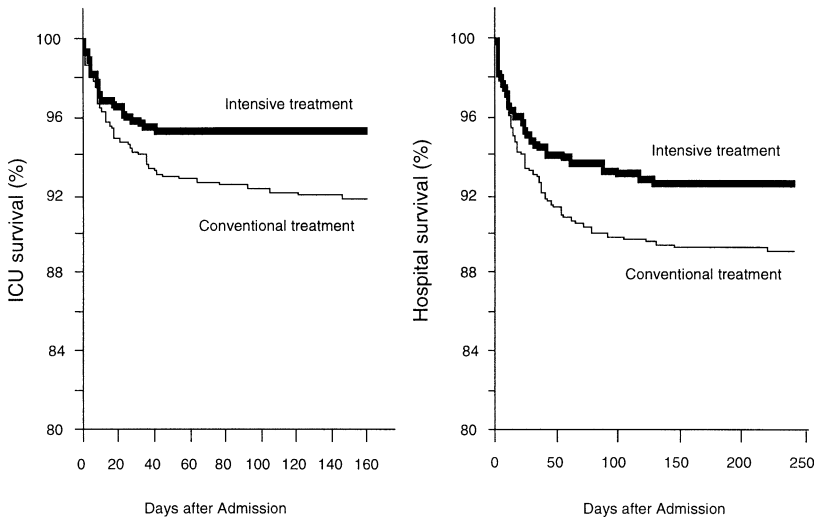

Fig. 8. Kaplan-Meier cumulative survival plots for intensive care and in-hospital survival, showing the effect of intensive insulin treatment in a study of 1548 critically ill patients. Patients discharged alive from intensive care (*left panel*) and hospital (*right panel*), respectively, were considered survivors. *P* values were obtained by logrank (Mantel-Cox) significance testing. The difference between the intensive insulin group and the conventional group was significant for intensive care survival (unadjusted $P = 0.005$; adjusted $P < 0.04$) and for hospital survival (unadjusted $P = 0.01$). (*From* Van den Berghe G, Wouters P, Weekes F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1357–67; with permission.)

Summary

Prolonged critical illness has a high morbidity and mortality. The acute and chronic phases of critical illness are associated with distinct endocrine alterations. The acute neuroendocrine response to critical illness involves an activated anterior pituitary function. In prolonged critical illness, however, a reduced pulsatile secretion of anterior pituitary hormones and the so-called "wasting syndrome" occur. The impaired pulsatile secretion of GH, thyrotropin and gonadotropin can be re-amplified by relevant combinations of releasing factors, which also substantially increase circulating levels of IGF-1, GH-dependent IGFBPs, thyroxin, tri-iodothyronine and testosterone. Anabolism is clearly re-initiated at the time GH secretagogues, thyrotropin-releasing hormone and gonadotropin-releasing hormone are coadministered but the effect on survival remains unknown. A lethal outcome of critical illness is predicted by a high serum concentration of IGFBP-1, pointing to impaired insulin effect rather than pituitary function, and survival was recently shown to be dramatically improved by strict normalization of glycemia with exogenous insulin.

In addition to the illness-induced endocrine alterations, patients may have pre-existing central or peripheral endocrine diseases, either previously diagnosed or unknown. Hence, endocrine function testing in a critically ill patient represents a major challenge and the issue of treatment remains controversial.

The recent progress in knowledge of the neuroendocrine response to critical illness and its interrelation with peripheral hormonal and metabolic alterations during stress, allows for potential new therapeutic perspectives to safely reverse the wasting syndrome and improve survival.

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