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Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma

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Abstract *Objective*: To study the time course of corticosteroid binding-globulin (CBG) level and the free cortisol index (FCI) in comparison with total cortisol and ACTH concentrations during acute and prolonged critical illness.
Design: Prospective observational clinical study.
Setting: Twenty-bed medical/surgical intensive care unit.
Patients and participants: Thirty patients with septic shock, eight patients with multitrauma, and forty healthy control subjects.
Measurements and results: During 14 days or until discharge/death, we serially measured serum concentrations of CBG, cortisol, TNF-α, IL-6, plasma ACTH immunoreactivity, and the FCI (= cortisol/CBG × 100). We also recorded haemodynamic parameters, APACHE II, ISS, SOFA scores, shock duration, inotrope use, and ICU mortality. In both groups we found markedly decreased CBG levels in the early phase (septic shock: 17.5 ± 5.9, and trauma: 16.1 ± 2.3 mg/l) in comparison with controls (37.3 ± 5.3 mg/l). The FCI was high in this early phase (septic shock: 7.2 ± 2.7; trauma: 6.5 ± 1.3; controls: 1.25 ± 0.76). During follow-up, CBG levels significantly increased, reaching normal levels from day 7 on. The FCI showed an opposite biphasic pattern, with near-normalising FCI values during the second phase. Regression analysis showed a negative correlation between CBG and IL-6 levels ($r_s = –0.63$; $P < 0.05$), but no relation between CBG concentrations and disease severity, shock duration or death was found.
Conclusions: We found extremely low CBG levels in early stage septic shock and multitrauma. These dramatic changes are reflected in a concomitant higher FCI, indicating a higher free cortisol level. A second phase displays increasing and normalising CBG levels, independent from clinical parameters. We believe that CBG plays an active role in the glucocorticoid response to severe stress and in the regulation of cortisol availability to target tissues.

Keywords ACTH · Corticosteroid-binding globulin · Free cortisol index · Interleukin-6 · Relative adrenal insufficiency · Septic shock · Multitrauma

Introduction

The activation of the hypothalamo-pituitary-adrenal (HPA) axis is considered as one of the most relevant elements of the stress responses during critical illness [1]. Acute and prolonged critical illness seem to be different neuroendocrine paradigms [2]. The acute response to severe illness or trauma consists primarily of an actively secreting anterior pituitary gland and a peripheral inactivation or inactivity of anabolic hormones. In the

chronic phase of critical illness, a uniformly reduced secretion of the different anterior pituitary hormones underlie impaired secretory activity of target tissues. Cortisol secretion appears to be a notable exception, being maintained through a peripheral drive [3].

Corticosteroid-binding globulin (CBG) or transcortin is the specific transport protein for serum cortisol [4, 5]. Cortisol roughly varies with CBG levels. CBG appears to exist in different tissues, to be involved in the control of corticosteroid uptake by cells, and to act as a biological significant signal [5], in addition to its classical role in controlling the amount of free corticosteroids in blood. Based on the free hormone theory, it is generally believed that only the free or unbound cortisol is biologically active [6]. By using the free cortisol index (FCI) an indirect indication of the unbound cortisol fraction can be derived easily [7]. In the face of changing CBG concentrations, it is unlikely that total cortisol measurements will accurately reflect the plasma profile of the free hormone and the true pituitary-adrenal activity, especially in low CBG states.

An obvious hypercortisolism is present in both acute and prolonged phases of critical illness, therefore we explored in both phases this important phenomenon by looking into the time course of CBG levels and FCI in a group of severely stressed patients with septic shock or multitrauma. In addition, we evaluated the relation of CBG and FCI with cytokines (TNF-α, IL-6), survival (ICU mortality), disease severity (APACHE II, SOFA), the clinical course (shock duration, inotrope use), renal and hepatic function, and the HPA-axis (total cortisol, ACTH).

Materials and methods

Patients

The study was performed at the Intensive Care Unit (ICU), Medical Spectrum Twente, Enschede, Netherlands, and approved by the Local Human Ethics Committee. Written informed consent from first-degree relatives was mandatory.

Thirty adult patients with septic shock and eight patients with multitrauma without head injury were included in the study within 6 h from admission to the ICU. Septic shock was defined by the following criteria: a documented infection or positive blood culture, at least two symptoms of a systemic inflammatory response syndrome such as fever (> 38 °C) or hypothermia (< 36 °C), tachycardia (> 90 beats/min), tachypnea (> 20 breaths/min), and abnormal white blood cell counts (> 12,000/μl or < 4,000/μl); use of vasopressor support despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction. Shock was defined as a decrease in systolic blood pressure to less than 90 mmHg, a drop of 40 mmHg from baseline [8]. The duration of shock, also the time the patient was in need of vasoactive drugs, was recorded in hours. Multitrauma patients were included when they had an Injury Severity Score (ISS) > 20.

Patients were excluded when there was a known abnormality of the HPA-axis, use of drugs influencing the HPA-axis, like corticosteroids, use of estrogens, pregnancy, burn wounds, unexplained hyper- or hypokalemia, age below 18 years or multitrauma with head injury.

Most patients with septic shock (n = 26) were invasively monitored by means of a Swan-Ganz catheter, when the treating intensivist decided it was clinically indicated. Patients were treated conventionally, including fluid resuscitation, antibiotics, vasopressor and positive inotropic therapy, mechanical ventilation and, in cases of acute renal failure, haemofiltration. The severity of diseases was assessed using the APACHE II scoring system, SOFA score or the ISS.

Healthy control subjects, whom were of similar age and sex (28 males and 12 females, mean age 59 years), were recruited from medical and laboratory staffs to create reference values.

Methods

Arterial blood samples were drawn daily at 6.00 a.m. Patients were included within 6 h from admission to ICU and/or diagnosis. Follow-up was done for 14 days, or until death or discharge from ICU. When (relative) adrenal insufficiency was suspected, defined as the presence of classical signs of adrenal insufficiency and/or unexplained hypotension and resistance to inappropriately high doses of vasoactive drugs, a short corticotropin stimulation test was performed (n = 8). Relative adrenal insufficiency was confirmed when a subnormal response to ACTH (cortisol increment < 200 nmol/l) and a post-stimulation cortisol level of < 550 nmol/l were found. Haemodynamic data were collected, as well as routine biochemistry and blood counts. Serum samples were stored at –30 °C until use. Serum cortisol was measured using a solid-phase chemiluminescent immunoassay (Diagnostic Products, Los Angeles, Calif., USA, Imulite). Serum CBG was determined with a time-resolved fluoroimmunoassay as published previously [7]. Further, we measured IL-6 and TNFα, both solid-phase, two-site chemiluminescent enzyme immunometric assays (Diagnostic Products).

The free cortisol index (FCI) was calculated by the formula: FCI = [cortisol (μmol/l)/CBG (mg/ml) × 100] [7]. In addition, free unbound cortisol was calculated from total cortisol and CBG using the Coolens method based on the binding equilibrium [9].

Statistical analysis

Values are expressed as mean ± SD. Serial data were analysed using a repeated measures analysis of variance on ranks followed by Dunn's test for specific comparisons. Two sample comparisons were performed using Mann Whitney U-test. Qualitative data were analyzed using the chi-square test. Spearman's rank order correlation coefficient (r_s) was used to evaluate the relations for individual data on each day of the study. A $P < 0.05$ was considered statistically significant. All analyses were performed using a statistical software package (SPSS 9.0.1).

Results

The clinical characteristics of the patients with septic shock and multitrauma are shown in Table 1. The patients with septic shock were older, more severely ill, had a longer ICU stay, and a higher mortality than the patients with multitrauma.

The biochemical data on admission to the ICU (Table 2) revealed distinct hypercortisolism in both pa-

Table 1 Clinical characteristics of patients with septic shock and multitrauma on admission. Values are mean ± SD

	Septic shock	Multitrauma	*P* value
Number	30	8	
Mean age	62 ± 11	52 ± 15	0.054
Sex (male/female)	20/10	7/1	< 0.05
APACHE II	16.2 ± 5.3	10.1 ± 2.9	< 0.01
SOFA	8.2 ± 3.2	4.2 ± 2.2	< 0.01
ISS	–	24 ± 4	
ICU survival *(n)*	19	8	< 0.01
Stay ICU (days)	30 ± 14	11 ± 5	< 0.01
Bacteremia *(n)*	19	0	< 0.01
Mechanical ventilation *(n)*	30	8	ns

Table 2 Laboratory data on admission in patients with septic shock or multitrauma and control subjects. Values are means ± SD. (*WBC* white blood count)

	Septic shock	Multitrauma	Controls
Cortisol (μmol/l)	1.09 ± 0.23[a]	1.03 ± 0.19[a]	0.32 ± 0.08
ACTH (pmol/l)	115.1 ± 29.2[a]	109.4 ± 36.2[a]	11.2 ± 4.5
CBG (ng/ml)	17.2 ± 5.9[a]	16.1 ± 3.2[a]	37.1 ± 5.3
Albumin (g/l)	25.1 ± 6.7[a]	28.3 ± 4.5[a]	38 ± 5
IL-6 (pmol/l)	1301 ± 377[a,b]	555 ± 256[a]	10.2 ± 4.8
TNF-α (pmol/l)	26.3 ± 9.6[a,b]	9.4 ± 2.1[a]	4.2 ± 2.2
FCI	7.2 ± 2.7[a]	6.5 ± 1.4[a]	1.25 ± 0.76
Calc. free cortisol (nmol/l)	294 ± 83[a]	275 ± 65[a]	23.5 ± 7.8
WBC ($\times 10^9$/l)	14.7 ± 8.2[a]	12.7 ± 4.2[a]	6.2 ± 2.5

[a]Patients versus controls; $P < 0.01$
[b]Septic shock versus multitrauma; $P < 0.01$

tient groups, with an appropriate increase in ACTH, and extremely low CBG levels in both groups (septic shock: 17.5 ± 5.9; trauma: 16.1 ± 2.3 mg/l), significantly lower than in healthy controls (37.3 ± 5.3 mg/l; $P < 0.01$). At the same time the FCI showed increased values at admission (septic shock: 7.2 ± 2.7; trauma: 6.5 ± 1.3 mg/l), also significantly different from healthy controls (1.25 ± 0.76 mg/l; $P < 0.01$). The IL-6 and TNF-α concentrations were increased in both patient groups, but much higher in septic patients (Table 2; $P < 0.01$).

The time course of CBG displayed a slowly increasing concentration, reaching normal levels after 6–7 days in both groups of patients (Fig. 1). The time course of FCI showed a mirror-like pattern with high values in the early phase and near-normalising values at the end of the observation period of 14 days (Fig. 2). The calculated free cortisol concentrations also showed high values on admission, which gradually decreased (but not significantly) in time, but never reached normal levels (Fig. 3). TNF-α concentrations did not show a specific pattern (data not shown), but IL-6 displayed extremely high levels on admission and a gradually decreasing pattern during follow-up ($P < 0.01$). Septic patients had higher IL-6 and TNF-α levels than multitrauma patients at all time points.

In septic patients IL-6 inversely correlated with CBG both on admission ($r_s = –0.63$; $P < 0.01$) (Fig. 4) and when all measurements were pooled ($r_s = –0.55$; $P < 0.01$). In multitrauma patients this correlation was absent (Fig. 4). Further regression analysis did not show any relation between CBG and other variables like APACHE II, ISS, leucocyte count, body temperature, TNF-α or ACTH (data not shown). In addition, no relation between CBG and serum creatinine and bilirubin was found.

The time course of SOFA scores showed a decreasing trend from 8.2 ± 3.2 on day 1 to 6.5 ± 3.6 on day 14. CBG had a weak inverse relation with the SOFA score ($r_s = –0.40$; $P = 0.054$) and the FCI a weak positive correlation ($r_s = 0.36$; $P = 0.06$), when data were pooled.

There was no relation between CBG levels and the duration of shock and inotrope use. CBG levels did not have a significant correlation with the mean arterial blood pressure (pooled data; $r_s = 0.33$, $P = 0.11$).

When looking at subgroups, non-survivors (all in the septic shock group) had comparable cortisol, ACTH, CBG, and FCI levels on admission as survivors. These subgroups only differed in IL-6, APACHE II, and SOFA scores (all higher in non-survivors; $P < 0.05$). During the course of septic shock these differences were still present.

Eight patients underwent ACTH testing; four of them had evidence of relative adrenal insufficiency and were successfully treated with hydrocortisone. The CBG levels and FCI values in these patients were comparable to the patients with ‘normal’ adrenal function.

Discussion

In reaction to an infectious or noxious insult, the host sets off an interactive network of simultaneously activated pathways, including activation of the HPA-axis resulting in secretion of adrenal glucocorticoids [10]. Glucocorticoids play an important role in mediating many of the physiological and pathophysiological effects of response to these harmful events. Glucocorticoids work in synergy to either eliminate or control the noxious insult and to repair any consequent tissue damage. Glucocorticoids inhibit the host defence response at virtually all levels, and their gradual and generalised suppressive influence protects the host from overreaction [11].

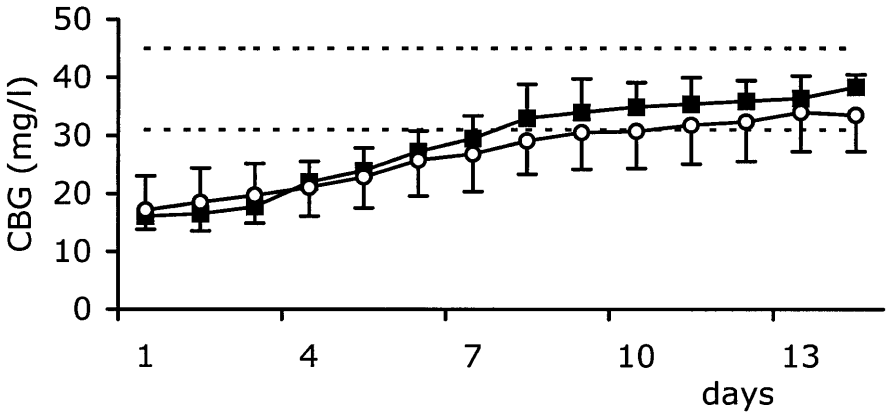

Fig. 1 The time course of cortisol binding globulin (CBG) concentrations in patients with septic shock (–o–) and multitrauma (—) during the observation period of 14 days. The range of normal values, derived from healthy volunteers, is displayed between *broken lines*

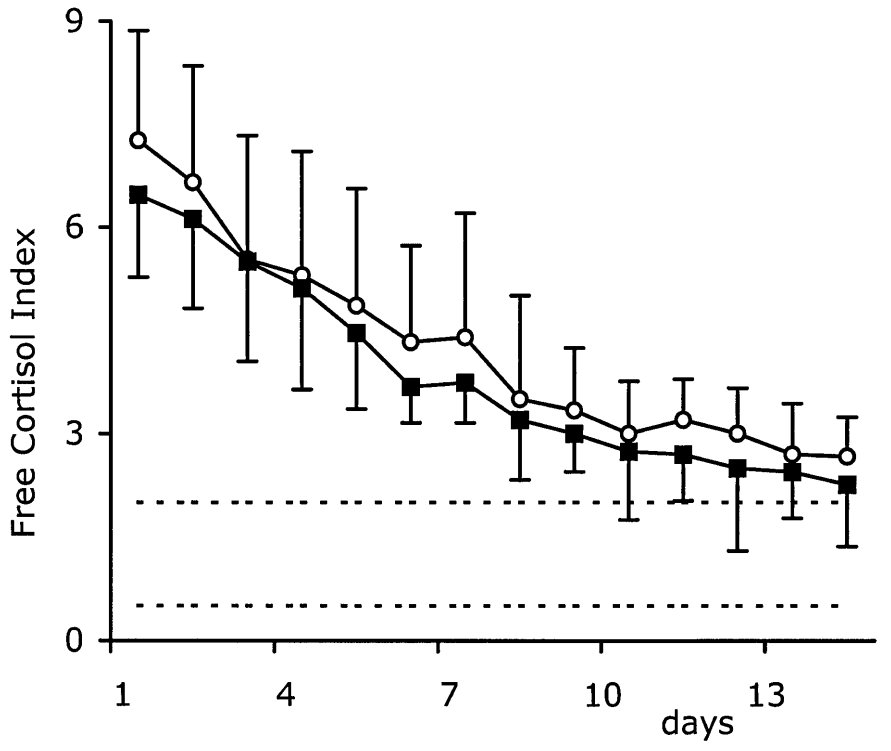

Fig. 2 The time course of the free cortisol index (FCI) in patients with septic shock (–o–) and multitrauma (—) during the observation period of 14 days. The range of normal values, derived from healthy persons, is displayed between *broken lines*

Critically ill patients have a wide range of cortisol concentrations that are usually increased, especially those with sepsis and septic shock [10, 12]. The appropriate plasma cortisol concentration in critically ill patients is not well known, and relative adrenal insufficiency may be present, in spite of high-normal cortisol concentrations [12, 13, 14]. High basal cortisol levels and a subnormal response to ACTH are indicative for fatal outcome [15]. However, the adrenal gland has an astonishing capacity to adapt to various forms of acute and chronic stress.

An important regulator of the amount of the biologically active free corticosteroid is CBG, a liver-derived plasma protein. In human plasma, CBG is the main carrier protein for cortisol (> 90 %), serving as a readily available reservoir of cortisol [4], but possibly has additional functions like facilitating steroid entry into the cell [5]. It is generally believed that the free fraction of cortisol is acting within target cells, where it initiates hormone actions, as stated by the free hormone theory [6].

Since cortisol half-life, pool size, and volume of distribution are determined largely by CBG, total plasma cortisol is not related to the cortisol production rate [16] when CBG varies [17]. Therefore, it is surprising that total cortisol is routinely measured, though the clinician would benefit from a free cortisol value to esti-

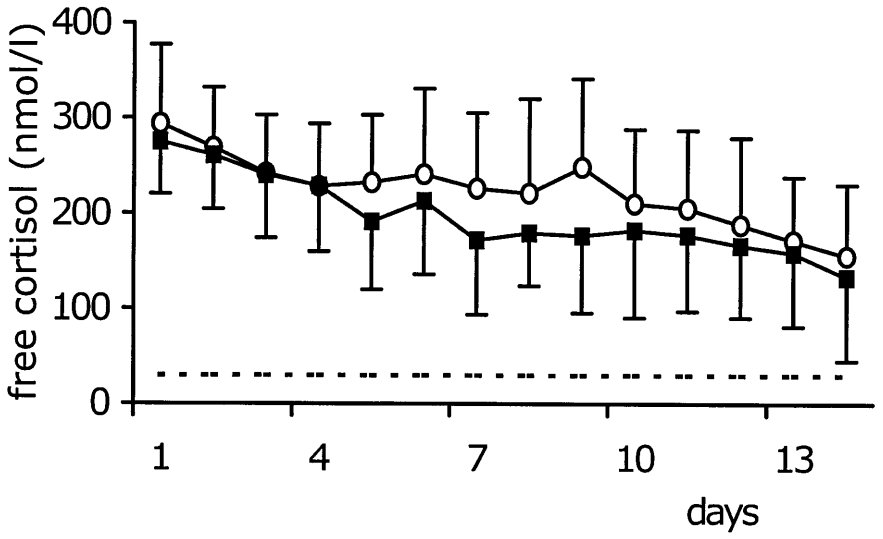

Fig. 3 The time course of calculated free cortisol concentrations in patients with septic shock (–o–) and multitrauma (—) during the observation period of 14 days. The upper limit of the normal values, derived from healthy persons, is displayed as a *broken line*

mate the biological importance of this hormone. The reference methods to measure free cortisol (ultrafiltration, equilibrium dialysis) are not feasible for routine use. The FCI, which can be calculated easily, might provide a suitable method to indirectly indicate free cortisol [7].

Changes in CBG production may importantly modulate corticosteroid action [18]. Several factors are known to substantially alter CBG levels. Glucocorticoids (both endogenous and synthetic) have an inhibitory effect on CBG production [19], thereby increasing the disposal of free cortisol to peripheral tissues as well as its volume of distribution [17]. Some conditions lead to a rise in CBG, e.g., estrogen therapy and lymphoproliferative malignancies [5]. CBG levels are relatively unaffected by a state of pre-existing malnutrition [20].

Our data show a remarkable biphasic pattern in CBG levels in both multitrauma and septic shock. The early phase shows extremely low CBG levels, which is also reflected by a concomitant higher FCI, indicating a relatively high free biologically active cortisol in the acute stress phase. The late phase, after 7–8 days, displays increasing and normalising CBG levels in both groups of patients, together with decreasing and almost normalis-

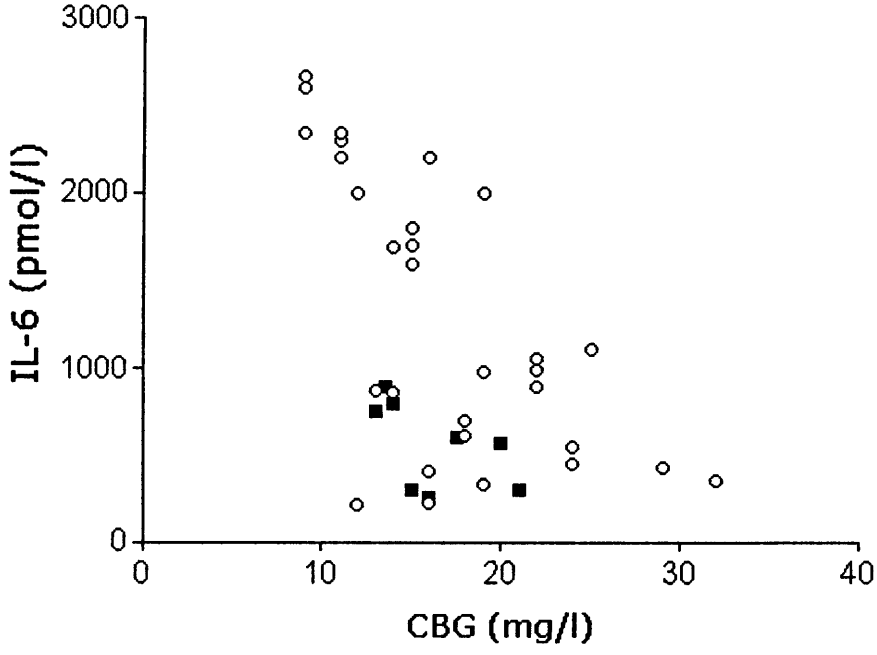

Fig. 4 Relation (Spearman's rank correlation coefficient, r_s) between serum CBG and plasma IL-6 levels on admission in patients with septic shock (o) and multitrauma (■). Septic patients: $n = 30$; $r_s = -0.63$, $P < 0.01$. Trauma patients: $n = 8$, $r_s = -0.50$, $P = 0.16$

ing FCI values. Savu et al. reported depletion of corticosteroid-binding activities during experimental inflammation [21] and during human septic shock [22]. The decrease of CBG during septic shock was associated with a low binding activity for cortisol in serum [23]. Perrot et al. also found low CBG levels and a high FCI in the acute phase of septic shock, but not in patients with non-septic shock [24]. Interestingly, dexamethasone infusion in all patients with shock showed that both total cortisol and free cortisol were not suppressible.

Several mechanisms are proposed to explain the CBG depletion during septic shock: increased metabolic clearance, decreased synthesis in the liver, or capillary leakage [5, 23]. Another theory to explain the low CBG concentration observed in sepsis is based on the fact that elastase, a serine protease that is released in large amounts from activated neutrophils present during acute infection, degrades CBG [5, 25, 26]. The CBG cleaved by elastase loses affinity for cortisol and, therefore, free cortisol can be released on the local site of the inflammation [25, 26, 27]. This possibly means a mechanism for the release of relatively large amounts of cortisol at sites of inflammation. The decrease of CBG concentration should not result in an increase of free cortisol if the negative feedback on ACTH secretion is normal. However, during critical illness this negative feedback is impaired [24, 28]. The absolute concentration of the free hormone will increase only if the cortisol secretion rate accelerates. This is because cortisol half-life, pool size and volume of distribution are inversely proportional to the concentration of CBG [17].

We are not aware of any reports regarding CBG levels in multitrauma patients. Our trauma patients showed a similar biphasic pattern as the patients with septic shock. Therefore, the acute decrease of CBG is not specific for septic shock, but probably reflects a stress-related phenomenon or immune activation, with CBG acting as a negative acute phase protein. This is supported by decreased CBG levels found in several non-sepsis conditions such as: a) certain stressors in experimental studies: tail shocks [29], immobilisation [30], restraint stress [30], fasting [31]; and b) clinical studies: burns [20] and post-cardiac surgery [32].

Interestingly, a relationship was found between serum levels of IL-6 and CBG in a group of patients with thermal burn injury [20, 33]. IL-6 is a pleiotropic cytokine with both pro- and anti-inflammatory effects [10], as well as the ability to activate the HPA-axis [34]. In these patients, CBG was decreased within 24 h and as a consequence the free fraction of cortisol was increased. IL-6 negatively correlated with both CBG and free cortisol, and it was hypothesised that IL-6 was (partly) responsible for the decrease of CBG. In addition, IL-6 was found to inhibit the production of CBG by human hepatoma-G2 cell in vitro [27, 35] and in healthy volunteers [36]. It was suggested that CBG was a negative acute phase protein. In our study we also found extremely high IL-6 levels in patients with septic shock, with a strong negative correlation to CBG ($r_s = -0.76$; $P < 0.01$). In patients with multitrauma, IL-6 levels were far lower, and no relation between IL-6 and CBG was present. Therefore, the regulation of CBG in multitrauma patients might be different than in septic patients, considering the difference in IL-6 levels. On the other hand, IL-6 may not be a major factor in the early decrease of circulating CBG, contrasting with other reports [33].

In the post-operative period after cardiac surgery, it was also demonstrated that CBG was depleted (50 %), resulting in very high free cortisol levels, calculated according to the equation described by Coolens et al. [9, 32]. Our data did not show correlation between CBG and calculated free cortisol. Calculated free cortisol was high in the early phase of critical illness, but only slowly decreased in time, normalising after 14 days. The Coolens method apparently has its limitations as normal albumin concentrations are assumed in the calculation, and because molar CBG concentrations clearly exceed that of cortisol [9]. However, as we found low albumin levels in most patients, we assume that no overestimation of free cortisol by the Coolens method is made.

Recent clinical trials on stress doses of hydrocortisone in patients with septic shock showed beneficial effects on hemodynamics [37, 38] and mortality [39]. These effects were not related to relative adrenal insufficiency in the study by Bollaert et al. [37], but in an as yet unpublished multicentre study nonresponders to ACTH showed a decrease in mortality [39]. Most studies mention increased total cortisol levels and, when considering our results, probably had increased free cortisol levels in the first days. Apparently, low doses of hydrocortisone are effective in spite of high levels of free cortisol. Whether this is related to relative adrenal insufficiency, alterations in glucorticoid receptors or glucocorticoid resistance is not clear, but a relative lack of cortisol for the tissue requirements is probably present [12]. We believe that calculated free cortisol permits a better evaluation of adrenocortical function and may provide insights for better diagnosis of adrenal insufficiency.

In conclusion, we found extremely low CBG levels in both early stage septic shock and multitrauma. These dramatic changes are reflected in a concomitant higher FCI, indicating higher unbound cortisol and revealing that when CBG is low the carrier protein becomes a major determinant of the concentration of free cortisol. A second phase, virtually present in all patients, shows increasing CBG levels, independent from clinical parameters. The exact mechanism to explain the early phase

CBG depletion is not well understood, but IL-6 might be responsible in septic patients. The finding that CBG was also diminished in the early phase of multitrauma supports CBG being a negative acute phase protein [21]. We believe that CBG plays an active role in the glucocorticoid response to severe stress, and should be considered a key element in the regulation of cortisol availability to target tissues.

References

1. Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332: 1351–1362
2. Van den Berghe G, De Zegher F, Bouillon R (1998) Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 83: 1827–1834
3. Vermes I, Beishuizen A, Hampsink RM, Haanen C (1995) Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab 80: 1238–1242
4. Dunn JF, Nisula BC, Rodbard D (1981) Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 53: 58–68
5. Rosner W (1990) The functions of corticosteroid-binding globulin and sex hormone- binding globulin: recent advances. Endocr Rev 11: 80–91
6. Ekins R (1990) Measurement of free hormones in blood. Endocr Rev 11: 5–46
7. Bonte HA, van den Hoven RJ, van der Sluijs Veer G, Vermes I (1999) The use of free cortisol index for laboratory assessment of pituitary-adrenal function. Clin Chem Lab Med 37: 127–132
8. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. Chest 101: 1644–1655
9. Coolens JL, Van Baelen H, Heyns W (1987) Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin. J Steroid Biochem 26: 197–202
10. Beishuizen A, Vermes I, Haanen C (1998) Endogenous mediators in sepsis and septic shock. Adv Clin Chem 33: 55–131
11. Munck A, Guyre PM, Holbrook NJ (1984) Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 5: 25–44
12. Matot I, Sprung CL (1998) Corticosteroids in septic shock: resurrection of the last rites? Crit Care Med 26: 627–630
13. Lamberts SWJ, Bruining HA, De Jong FH (1997) Drug therapy: corticosteroid therapy in severe illness. N Engl J Med 337: 1285–1292
14. Beishuizen A, Vermes I, Hylkema BS, Haanen C (1999) Relative eosinophilia and functional adrenal insufficiency in critically ill patients. Lancet 353: 1675–1676
15. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Belissant E (2000). A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 283: 1038–1045
16. Melby JC, Spink WW (1958). Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. 37: 1791–1798
17. Bright GM (1995) Corticosteroid-binding globulin influences kinetic parameters of plasma cortisol transport and clearance. J Clin Endocrinol Metab 80: 770–775
18. Bright GM, Darmaun D (1995) Corticosteroid-binding globulin modulates cortisol concentration responses to a given production rate. J Clin Endocrinol Metab 80: 764–769
19. Schlechte JA, Hamilton D (1987) The effect of glucocorticoids on corticosteroid binding globulin. Clin Endocrinol 27: 197–203
20. Garrel DR (1996) Corticosteroid-binding globulin during inflammation and burn injury: nutritional modulation and clinical implications. Horm Res 45: 245–251
21. Savu L, Lombart C, Nunez EA (1980) Corticosterone binding globulin: an acute phase "negative" protein in the rat. FEBS Lett 113: 102–106
22. Savu L, Zouaghi H, Carli A, Nunez EA (1981) Serum depletion of corticosteroid binding activities, an early marker of human septic shock. Biochem Biophys Res Commun 102: 411–419
23. Pugeat M, Bonneton A, Perrot D, Rocle-Nicolas B, Lejeune H, Grenot C, Dechaud H, Brebant C, Motin J, Cuilleron CY (1989) Decreased immunoreactivity and binding activity of corticosteroid- binding globulin in serum in septic shock. Clin Chem 35: 1675–1679
24. Perrot D, Bonneton A, Dechaud H, Motin J, Pugeat M (1993). Hypercortisolism in septic shock is not suppressible by dexamethasone infusion. Crit Care Med 21: 396–401
25. Pemberton PA, Stein PE, Pepys MB, Potter JM, Carrell RW (1988) Hormone binding globulins undergo serpin conformational change in inflammation. Nature 336: 257–258
26. Hammond GL, Smith CL, Paterson NA, Sibbald WJ (1990) A role for corticosteroid-binding globulin in delivery of cortisol to activated neutrophils. J Clin Endocrinol Metab 71: 34–39
27. Bartalena L, Hammond GL, Farsetti A, Flink IL, Robbins J (1993) Interleukin-6 inhibits corticosteroid-binding globulin synthesis by human hepatoblastoma-derived (Hep G2) cells. Endocrinology 133: 291–296
28. Reincke M, Allolio B, Würth G, Winkelmann W (1993) The hypothalamic-pituitary-adrenal axis in critical illness: response to dexamethasone and corticotropin releasing hormone. J Clin Endocrinol Metabol 77: 151–156
29. Fleshner M, Deak T, Spencer RL, Laudenslager ML, Watkins LR, Maier SF (1995) A long-term increase in basal levels of corticosterone and a decrease in corticosteroid-binding globulin after acute stressor exposure. Endocrinology 136: 5336–5342
30. Tannenbaum B, Rowe W, Sharma S, Diorio J, Steverman A, Walker M, Meaney MJ (1997) Dynamic variations in plasma corticosteroid-binding globulin and basal HPA activity following acute stress in adult rats. J Neuroendocrinol 9: 163–168

31. Tinnikov AA (1999) Responses of serum corticosterone and corticosteroid-binding lobulin to acute and prolonged stress in the rat. Endocrine 11: 145–150
32. Vogeser M, Felbinger TW, Kilger E, Roll W, Fraunberger P, Jacob K (1999) Corticosteroid-binding globulin and free cortisol in the early postoperative period after cardiac surgery. Clin Biochem 32: 213–216
33. Bernier J, Jobin N, Emptoz-Bonneton A, Pugeat MM, Garrel DR (1998) Decreased corticosteroid-binding globulin in burn patients: relationship with interleukin-6 and fat in nutritional support. Crit Care Med 26: 452–460
34. Bethin KE, Vogt SK, Muglia LJ (2000) Interleukin-6 is an essential, corticotropin-releasing hormone- independent stimulator of the adrenal axis during immune system activation. Proc Natl Acad Sci USA 97: 9317–9322
35. Emptoz-Bonneton A, Crave JC, Le-Jeune H, Brebant C, Pugeat M (1997) Corticosteroid-binding globulin synthesis regulation by cytokines and glucocorticoids in human hepatoblastoma-derived (HepG2) cells. J Clin Endocrinol Metab 82: 3758–3762
36. Tsigos C, Kyrou I, Chrousos GP, Papanicolaou DA (1998) Prolonged suppression of corticosteroid-binding globulin by recombinant human interleukin-6 in man. J Clin Endocrinol Metab 83: 3379
37. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A (1998). Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26: 645–650
38. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G (1999). Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double blind, single-centre study. Crit Care Med 27: 723–732
39. Annane D (2000). Effects of the combination of hydrocortisone-fludrocortisone on mortality in septic shock. Crit Care Med 28:A63