

CLINICAL STUDY

Hypothalamic–pituitary–adrenal axis response to the severity of illness in non-critically ill patients: does relative corticosteroid insufficiency exist?

M Michalaki¹, T Margeli¹, A Tsekouras¹, C H Gogos², A G Vagenakis¹ and V Kyriazopoulou¹

¹Division of Endocrinology, Department of Medicine and ²Division of Internal Medicine, University Hospital of Patras, Patras 26500, Greece

(Correspondence should be addressed to V Kyriazopoulou; Email: vkyriazopoulou@med.upatras.gr)

Abstract

Objective: Relative corticosteroid insufficiency may be common in critically ill patients and is associated with a poor outcome; however, the response of the hypothalamic–pituitary–adrenal (HPA) axis in nursed patients is not known. Our aim was to evaluate the response of HPA axis to the severity of illness in non-critically ill nursed (NCIN) patients and the clinical outcome.

Subjects and methods: Fifty-six nursed patients who were divided into four groups (stroke, mild disease, sepsis and severe sepsis) as well as a control group ($n = 15$) were studied. At admission (day 1), cortisol and ACTH were measured and a low-dose (1 μg) corticotrophin test was performed, followed 2 h later by a standard-dose (250 μg) corticotrophin test. Diurnal variation of cortisol was obtained on day 2. A second identical set of low-dose and standard-dose corticotrophin tests were performed on day 5 or 6 (recovery phase).

Results: In patients with stroke and severe sepsis, cortisol had the highest values and its diurnal variation was abolished. Dissociation of ACTH and cortisol was found in all patients.

The Δ_{max} of cortisol after the 1- μg corticotrophin test did not differ among the groups, while after the 250- μg corticotrophin test, it was borderline higher in controls. The ratio of responders (Δ_{max} of cortisol ≥ 9 $\mu\text{g}/\text{dl}$) to non-responders after 1- or 250- μg corticotrophin test did not differ among patients and controls. All patients had a good outcome without glucocorticoid treatment.

Conclusions: Depending on the severity of illness, mild alterations in the HPA axis occurred. However, relative corticosteroid insufficiency was not confirmed in NCIN patients.

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Introduction

Illness of various degrees of severity and hospital care result in a stress response, which is mainly mediated by the hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal system (1, 2). Although an increasing number of studies have been performed on the function of the axis during illness (3, 4), the effectiveness of the axis in severity of illness with respect to cortisol secretion remains unclear. In addition, the use of cortisol treatment in accordance with the severity of illness, especially in acute phase, is controversial. It remains to be established if the administration of glucocorticoids that improves the outcome of critically ill patients (5, 6) also improves the outcome of non-critically ill nursed (NCIN) patients.

A consensus statement was published recently with regard to the diagnosis and management of corticosteroid deficiency in patients with critical illness (critical illness-related corticosteroid insufficiency, CIRCI) by an international task force of the American College of Critical Care Medicine (7). According to the

task force, the recommendations for treatment with corticosteroids are limited to septic shock and acute respiratory distress syndrome (ARDS).

CIRCI is caused by adrenal insufficiency and tissue resistance to corticosteroids, and it is characterized by an exaggerated and protracted proinflammatory response (1). The diagnosis of tissue resistance to corticosteroid is difficult (8). According to Annane *et al.* (9), the best criteria for the diagnosis of adrenal insufficiency in critically ill patients are an increase in total serum cortisol of < 9 $\mu\text{g}/\text{dl}$ after the administration of corticotrophin (250 μg) or a random total cortisol measurement of < 10 $\mu\text{g}/\text{dl}$. However, a current concept by Bornstein (10) suggested that the best available test for the diagnosis of adrenal insufficiency in critical illness is the 1- μg corticotrophin stimulation test. However, although this test is more sensitive, it is not accepted by all (7, 9).

Review of the extensive literature in this area highlights several important unresolved issues with respect to the function of the HPA axis both in physiological states and under the stress of illness. It is

not established if the above-mentioned diagnostic criteria for CIRCI could be used in NCIN patients and if the dysfunction of the HPA axis could determine the clinical outcome.

It is well documented that glucocorticoid synthesis and release by the adrenal glands are regulated by the HPA axis. However, the picture has subsequently become more complex, and it seems that although ACTH is essential for this release, alternative pathways exist for the regulation of adrenocortical function. Dissociation between the levels of ACTH and glucocorticoids during foetal, postnatal and adult life has been demonstrated (11, 12). In addition, clinical studies report the dissociation of ACTH and glucocorticoid levels in critical illness, inflammation and mental disorders. Cytokines, vasoactive factors and neuropeptides seem to play an important role in the modulation of the adrenal response to severe stress, and act independently of ACTH (12).

There is a need for more research to evaluate the adrenal response to the severity of illness in the acute and recovery phases in NCIN patients to detect if relative corticosteroid insufficiency exists, as well as the need for glucocorticoid treatment.

Subjects and methods

This is a prospective study performed between September 2007 and October 2008 in the Department of Internal Medicine of the University Hospital of Patras. Fifty-six patients who had been admitted to the hospital were divided into four groups according to the severity of their illness: group 1 comprised ten patients (seven males/three females) with ischaemic stroke as diagnosed by computed tomography. Patients with transient ischaemic attack were excluded. Group 1 patients had a mean age of 68.5 ± 7.8 years and a mean body mass index (BMI) of 25.1 ± 3.2 kg/m²; group 2 comprised 15 patients (7 males/8 females) with respiratory or urinary track infections (defined as mild disease) and they had a mean age of 62.4 ± 13.8 years and a mean BMI of 27.5 ± 3.9 kg/m²; group 3 comprised 20 patients (8 males/12 females) with sepsis and they had a mean age of 58.5 ± 8.9 years and a mean BMI of 25.6 ± 5.6 kg/m² and group 4 comprised 11 patients (5 males/6 females) with severe sepsis and they had a mean age of 61.3 ± 9.3 years and a mean BMI of 26.2 ± 4 kg/m². Fifteen healthy controls (seven males/eight females) were also evaluated (mean age 59.6 ± 5.1 years; mean BMI 26.1 ± 2.2 kg/m²). The controls (group 5) were recruited from the endocrinology outpatient clinic, and were mainly staff members, relatives or friends who were exposed to the stressful conditions of the hospital.

Sepsis was defined as the clinical syndrome of systemic inflammatory response (SIRS) with suspected or proven microbial aetiology. SIRS was diagnosed

based on two or more of the following conditions: fever (temperature > 38 °C) or hypothermia (temperature < 36 °C), tachycardia (> 90 beats/min), tachypnoea (> 24 breaths/min), leucocytosis or leucopaenia (white blood cells $> 12\ 000$ or < 4000 cells/ μ l respectively) or immature neutrophils (bands $> 10\%$) (13). Severe sepsis was defined as sepsis with one or more signs of organ dysfunction as follows: i) *Cardiovascular*: arterial systolic blood pressure ≤ 90 mmHg or mean arterial pressure ≤ 70 mmHg that responded to administration of intravenous fluid. ii) *Renal*: urine output < 0.5 ml/kg per h for 1 h despite adequate fluid resuscitation. iii) *Respiratory*: PaO₂/FiO₂ ≤ 250 or, if the lung was the only dysfunctional organ, ≤ 200 . iv) *Haematological*: platelet count $< 80\ 000/\mu$ l or 50% decrease in platelet count from the highest value recorded over the previous 3 days. v) *Unexplained metabolic acidosis*: a pH ≤ 7.30 or a base deficit ≥ 5.0 mEq/l and a plasma lactate level > 1.5 times the upper limit of normal for the reporting laboratory. vi) *Adequate fluid resuscitation*: pulmonary artery wedge pressure ≥ 12 mmHg or central venous pressure ≥ 8 mmHg (13). Severe sepsis was evaluated using the sepsis-related organ failure assessment (SOFA) score (14).

No patients had a history of adrenal insufficiency and they had not received any drug known to affect the HPA axis such as rifampicine (15, 16), ketoconazole (17), or other antifungal agents or anticonvulsants (18). The patients did not receive corticosteroids, including inhaled preparations, or catecholamines during the study.

Informed written consent was obtained, and the study protocol was approved by the ethics committee of the hospital.

Study design

On admission (day 1), a blood count and biochemical tests were performed, and baseline serum samples for cortisol, triiodothyronine (T₃), thyroxine (T₄), and TSH, and a plasma sample for ACTH were obtained from each patient (baseline values). Also on admission, each patient had undergone a low-dose (1 μ g) corticotrophin test and 2 h later a standard-dose (250 μ g) corticotrophin test (tetracosactrin 0.25 mg, Synacthen; Ciba-Geigy, Rueil-Malmaison, France). The tests were performed as follows: after a baseline serum cortisol concentration was drawn, the low-dose corticotrophin test was performed by administering 1 μ g corticotrophin intravenously. Samples for the measurements of serum cortisol were obtained at 30 (t30) and 60 (t60) minutes after injection. Two hours after the low-dose corticotrophin test, the standard-dose (250 μ g) corticotrophin test was performed by administering 250 μ g corticotrophin intravenously. Samples for the measurements of serum cortisol were taken at t30 and t60 (19). The cortisol response (Δ_{\max}) was defined as the highest cortisol concentration at t30 or t60 minus the baseline

serum cortisol. Responders were classified as patients with $\Delta_{\max} > 9 \mu\text{g/dl}$, and non-responders were classified as the subjects with $\Delta_{\max} \leq 9 \mu\text{g/dl}$.

On day 2, samples were collected from each patient for the measurements of serum cortisol at 0800, 1400, 2000 and 0200 h.

Healthy controls who attended the hospital for 1 day underwent identical low-dose (1 μg) and standard-dose (250 μg) corticotrophin tests.

Three out of the 11 patients with severe sepsis (group 4) died on day 3 or 4. These patients were transferred to the intensive care because of the deterioration of their condition after admission, and no further tests were performed after day 1.

On day 5 or 6 of nursing, during recovery, 7 of 20 patients with sepsis (group 3) and the 8 survivors with severe sepsis (group 4) were tested again with the low-dose (1 μg) and standard-dose (250 μg) corticotrophin tests.

Assays

Serum samples were centrifuged immediately, aliquoted and stored at -70°C until assayed. Plasma samples for the measurement of ACTH were collected under chilled conditions and centrifuged in a cooled centrifuge. Serum cortisol, thyroid hormones and plasma ACTH were measured by chemiluminescence immunoassay (Modular Analytics E170, Roche, and Hitachi). The samples were assayed in a single large batch. For cortisol, the within- and between-run coefficient of variation (CV) values were 1.5–1.7 and 1.8–2.8%, and the lower detection limit was 0.018 $\mu\text{g/dl}$. For ACTH, the within- and between-run CV values were 0.6–2.7 and 3.5–5.4%, and the lower detection limit was 1.0 pg/ml . For T_3 , T_4 and TSH respectively the within- and between-run CV values were 1.5–3.1 and

1.3–1.7%, 1.1–3.0 and 3.7–4.5% and 3.4–4.2 and 3.3–7.2% and the lower detection limits were 0.195 ng/ml , 0.42 $\mu\text{g/dl}$ and 0.005 $\mu\text{U/ml}$.

Statistical analysis

All values are expressed as the mean \pm s.d., and statistical significance was set at $P < 0.05$. Mean values were compared between groups by one-way ANOVA and *post hoc* analysis using the Bonferroni multiple comparison test, or independent-samples *t*-tests. Mean values within groups were compared by ANOVA for repeated measurements or paired *t*-tests. For categorical variables, comparisons between groups were performed using the χ^2 or Fisher's exact test. Pearson's correlation tests were used to assess the relationships among several parameters. Data were analyzed with the use of SPSS version 16 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline measurements and low- and standard-dose corticotrophin tests on day 1

No differences were detected among the groups with respect to age, BMI or gender. Baseline measurements from all groups are presented in Table 1. Mean serum ACTH levels did not differ among the groups, but the mean serum cortisol levels were significantly different (one-way ANOVA, $P < 0.001$). *Post hoc* analysis revealed that the mean cortisol levels in group 4 were higher than those in groups 2, 3 and 5 ($P < 0.001$), but they did not differ from that in group 1. Mean albumin levels differed among groups (one-way ANOVA, $P < 0.001$), and the lowest value was obtained in group 4 (*post hoc* analysis, $P < 0.001$). Mean serum T_4 and TSH did not differ among the groups, whereas the T_3 levels were

Table 1 Baseline characteristics and cortisol response to low and standard doses of ACTH in five groups of participants at admission (day 1).

	Ischaemic stroke (group 1; n=10)	Mild disease (group 2; n=15)	Sepsis (group 3; n=20)	Severe sepsis (group 4; n=11)	Controls (group 5; n=15)	P
Cortisol ($\mu\text{g/dl}$)	24.4 \pm 9.37	19.7 \pm 6.5	21.8 \pm 7.1	38.01 \pm 24.9	13.1 \pm 5.9	<0.001
ACTH (pg/ml)	13.6 \pm 9.7	14.7 \pm 10.5	18.3 \pm 7.2	11.2 \pm 12.7	19.3 \pm 10.6	NS
T_3 (ng/ml)	0.9 \pm 0.3	0.9 \pm 0.2	0.8 \pm 0.19	0.58 \pm 0.12	1.3 \pm 0.24	<0.001
T_4 ($\mu\text{g/dl}$)	8.2 \pm 1.3	8.9 \pm 1.4	7.4 \pm 1.7	7.8 \pm 2.0	8.2 \pm 1.7	NS
TSH ($\mu\text{U/ml}$)	1.6 \pm 1.1	1.3 \pm 1.2	0.98 \pm 0.6	1.5 \pm 1.4	1.9 \pm 1.02	NS
Albumin (g/dl)	3.7 \pm 0.5	3.6 \pm 0.4	3.5 \pm 0.5	2.5 \pm 0.6	4.4 \pm 0.2	<0.001
$\Delta_{\max-1 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	12.3 \pm 6.9	10.9 \pm 4.9	10 \pm 4.1	10.06 \pm 5.06	13.8 \pm 4.6	NS
$\Delta_{\max-250 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	21.7 \pm 9.2	18 \pm 7.1	17.01 \pm 6.6	16.35 \pm 7.8	23.9 \pm 8.5	0.05
Responders/non-responders after 1 $\mu\text{g ACTH}$	7/3	9/6	12/8	7/4	13/2	NS
Responders/non-responders after 250 $\mu\text{g ACTH}$	9/1	15/0	18/2	9/2	15/0	NS

Group 1, ischaemic stroke; group 2, mild disease; group 3, sepsis; group 4, severe sepsis; group 5, controls. Δ_{\max} of cortisol maximum–cortisol baseline; $\Delta_{\max-1 \mu\text{g ACTH}}$, Δ_{\max} after 1 $\mu\text{g ACTH}$; $\Delta_{\max-250 \mu\text{g ACTH}}$, Δ_{\max} after 250 $\mu\text{g ACTH}$; Responders, $\Delta_{\max} > 9 \mu\text{g/dl}$.

significantly different (one-way ANOVA, $P < 0.001$). *Post hoc* analysis showed that the mean T_3 levels in group 4 were lower than those in the other groups ($P < 0.05$ and $P < 0.001$ respectively).

Mean serum cortisol levels at the baseline did not correlate with the mean ACTH levels in all groups of patients, but they did correlate with the SOFA score in group 4 (Pearson $r = 0.77$, $P < 0.001$), and they were inversely correlated with the mean T_3 levels in all patient groups (Pearson $r = -0.39$, $P < 0.001$).

The Δ_{\max} of cortisol after the 1- μg corticotrophin test did not differ among the groups. However, the differences in Δ_{\max} of cortisol after the 250- μg corticotrophin test were borderline significant ($P = 0.05$). The Δ_{\max} of cortisol after the 250- μg corticotrophin test tended to be higher in the control group than in patients with sepsis or severe sepsis (independent-samples *t*-test, $P < 0.05$).

The Δ_{\max} of cortisol was higher after the 250- μg corticotrophin test than after the 1- μg corticotrophin test in all groups of patients (paired *t*-tests, $P < 0.001$) and in healthy controls (paired *t*-tests, $P < 0.01$). The Δ_{\max} of cortisol was inversely correlated with baseline cortisol after the 1 and 250- μg corticotrophin tests. (Pearson $r = -0.475$, $P < 0.001$; Pearson $r = -0.335$, $P < 0.05$ respectively).

Baseline characteristics of the responders and non-responders in all groups for both low- and standard-dose corticotrophin tests are presented in Table 1.

The baseline characteristics of the three patients with severe sepsis who died on the 3rd and 4th days of hospitalization are presented in Table 2.

During nursing, none of the patients developed hypotension or any electrolyte disorders.

Circadian rhythm

The diurnal variation in serum cortisol disappeared in groups 1 and 4, but it was maintained in groups 2 and 3 (Table 3). In the four groups of patients, the mean serum cortisol at midnight was $> 2.5 \mu\text{g/dl}$, which is the normal level of cortisol in subjects who are awake (20).

Table 2 Baseline characteristics and cortisol response to low and standard doses of ACTH at admission (day 1) in three non-survivors with severe sepsis (group 4).

	Patient 1	Patient 2	Patient 3
Cortisol ($\mu\text{g/dl}$)	41.5	63.4	100.5
ACTH (pg/ml)	14.8	1.02	1.00
T_3 (ng/ml)	0.41	0.42	0.6
T_4 ($\mu\text{g/dl}$)	8.1	7.7	4.1
TSH ($\mu\text{U/ml}$)	0.76	0.82	0.005
Albumin (g/dl)	2.8	1.8	2
$\Delta_{\max-1 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	9.34	7.3	2.4
$\Delta_{\max-250 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	17.7	6.9	1.8

Table 3 Circadian rhythm of serum cortisol on the first day after admission (day 2) in four groups of patients. ANOVA for repeated measurements was performed in each group. Values are expressed as the mean \pm s.d.

	Ischaemic stroke (group 1; $n = 10$)	Mild disease (group 2; $n = 15$)	Sepsis (group 3; $n = 20$)	Severe sepsis (group 4; $n = 11$)
Cortisol 0800 ($\mu\text{g/dl}$)	27.6 \pm 14.6	19.7 \pm 6.9	27.3 \pm 6	48.04 \pm 24.94
Cortisol 1400 ($\mu\text{g/dl}$)	26.7 \pm 10.1	16 \pm 6.4	23.9 \pm 7.6	42.1 \pm 24.6
Cortisol 2000 ($\mu\text{g/dl}$)	22.5 \pm 8.4	13.8 \pm 6.5	17.6 \pm 6.4	42.5 \pm 23.8
Cortisol 0200 ($\mu\text{g/dl}$)	20.6 \pm 10.2	10.3 \pm 5.2	13.7 \pm 5.3	38.9 \pm 25.5
<i>P</i>	NS	< 0.001	< 0.001	NS

Cortisol response to both the low- and standard-dose corticotrophin tests in patients with sepsis and severe sepsis during acute and recovery phases of illness

On day 5 or 6 during recovery, 7 of 20 patients with sepsis (group 3) and 8 survivors with severe sepsis (group 4) underwent additional testing with the low-dose (1 μg) and standard-dose (250 μg) corticotrophin tests.

In the patients in group 3, the mean serum cortisol levels were slightly higher in the acute phase than in the recovery phase ($P = 0.07$), whereas the mean plasma ACTH levels did not differ. The Δ_{\max} of cortisol level after the 1- μg corticotrophin test did not differ between the acute phase of illness (day 1) and the recovery phase (day 5 or 6). However, Δ_{\max} of cortisol after the 250- μg corticotrophin test was significantly higher in the recovery phase (Table 4).

The patients from group 4 who survived had mean cortisol levels that were higher in the acute phase than in the recovery phase, whereas their mean plasma ACTH and Δ_{\max} of cortisol after both corticotrophin tests did not differ between the acute and recovery phases (Table 5).

Table 4 Mean cortisol, ACTH, $\Delta_{\max-1 \mu\text{g ACTH}}$ and $\Delta_{\max-250 \mu\text{g ACTH}}$ at baseline (acute phase) and on the 5th or 6th day of hospitalization (recovery phase) in seven patients with sepsis.

	Acute phase	Recovery phase	<i>P</i>
Cortisol ($\mu\text{g/dl}$)	22.8 \pm 5.8	16.4 \pm 7.7	0.07
ACTH (pg/ml)	18.1 \pm 9.2	16.5 \pm 7.8	NS
$\Delta_{\max-1 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	9.5 \pm 2.6	11.7 \pm 3.9	NS
$\Delta_{\max-250 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	14 \pm 5.4	19.7 \pm 3.3	< 0.001
Responders/non-responders after 1 $\mu\text{g ACTH}$	4/3	5/2	NS
Responders/non-responders after 250 $\mu\text{g ACTH}$	6/1	7/0	NS

Table 5 Mean cortisol, ACTH, $\Delta_{\max-1 \mu\text{g ACTH}}$ and $\Delta_{\max-250 \mu\text{g ACTH}}$ at baseline (acute phase) and on the 5th or 6th day of hospitalization (recovery phase) in eight survivors with severe sepsis.

	Acute phase	Recovery phase	P
Cortisol ($\mu\text{g/dl}$)	26.59 \pm 9.4	18.8 \pm 8.2	<0.05
ACTH (pg/ml)	11.45 \pm 4.98	20.3 \pm 13.8	NS
$\Delta_{\max-1 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	11.5 \pm 5	11.3 \pm 3.9	NS
$\Delta_{\max-250 \mu\text{g ACTH}}$ ($\mu\text{g/dl}$)	19.2 \pm 5.85	20.04 \pm 8.9	NS
Responders/non-responders after 1 $\mu\text{g ACTH}$	6/2	5/3	NS
Responders/non-responders after 250 $\mu\text{g ACTH}$	8/0	8/0	NS

Discussion

The HPA axis is strongly activated by the stress of illness depending on its severity, and this results in the release of cortisol from the adrenal cortex (1, 2 and 7). This activation is crucial for the general adaptation to illness and the maintenance of the physiological response of organs.

Pituitary ACTH is essential for adrenocortical function, but alternative ACTH-independent pathways seem to play a significant role in corticosteroid secretion, especially under conditions of stress. This results in dissociation between plasma levels of ACTH and corticosteroids (11, 12).

Numerous recent studies have indicated that neuropeptides, neurotransmitters, cytokines, adipokines and growth factors modulate adrenal glucocorticoid release independently of ACTH, but the exact mechanisms remain unknown (12). Our results are in accordance with the previous observations. This study confirmed the dissociation between plasma ACTH level and serum cortisol level in all four groups of NCIN patients, and a correlation of serum cortisol level with SOFA score was found. This suggests that the cytokines produced in sepsis and severe sepsis are responsible for adrenocortical activation and cortisol production despite the relatively low levels of plasma ACTH.

The mean serum cortisol level at baseline in patients with severe sepsis was significantly higher than that in the other groups of NCIN patients and was positively correlated with SOFA score. They also had a lower level of albumin, which leads to even higher levels of free cortisol (21). This finding indicates an appropriate stimulation of the HPA axis and proportional cortisol production, which are enough for the general adaptation to this specific illness. The fact that the serum cortisol of the three patients with severe sepsis who were transferred to the intensive care unit and died was very high and two of them had Δ_{\max} of cortisol $< 9 \mu\text{g/dl}$ after the low-dose (1 μg) and standard-dose (250 μg) corticotrophin tests is interesting. These findings are in accordance with those obtained by Annane (22) who

reported that the incidence of mortality is higher in patients with critical illness who have a random cortisol level above 34 $\mu\text{g/dl}$ and Δ_{\max} of cortisol $\leq 9 \mu\text{g/dl}$. Our opinion is that such an extremely high level of serum cortisol could be a prognostic criterion for an increased mortality rate in nursed patients with severe sepsis.

The diurnal variation in serum cortisol level was abolished in group 1 which corresponded to patients with ischaemic stroke and group 4 with patients with severe sepsis. High levels of serum cortisol were found in these patients during the day, which was probably a response of the activated HPA axis to the stress of illness. It is remarkable that patients with stroke or severe sepsis have the same response to the stress of illness. In group 2, which corresponded to patients with mild disease, and group 3, which corresponded to patients with sepsis, although a diurnal variation in serum cortisol was maintained, the level of cortisol at midnight remained high compared with that in normal unstressed subjects (20).

We observed that the healthy subjects in the control group had a Δ_{\max} of cortisol after the 250- μg corticotrophin stimulation test which was marginally higher than that in patients with sepsis or severe sepsis. We speculated what is the level of Δ_{\max} of cortisol after the 250- μg corticotrophin stimulation test expected in disease and particularly in sepsis and severe sepsis taking into account the already maximum stimulation of the HPA axis.

The ratio of responders to non-responders after the low- or standard-dose corticotrophin tests did not differ among the patient groups and healthy controls. This is a finding of high importance, and it supports the fact that the Δ_{\max} of cortisol $< 9 \mu\text{g/dl}$ after the standard-dose corticotrophin test could not be a diagnostic criterion for relative corticosteroid insufficiency in non-critically ill patients. We believe that further studies with a lot of patients with different severity of illness are needed to confirm the appropriate baseline and stimulated cortisol levels in non-critically ill patients, by taking into account the various needs of each patient also, a fact which is very complicated.

The acute stress response during critical illness is characterized by activation of the HPA axis and sympathoadrenal system axis, with increased secretion of cortisol, an increase in the percentage of free cortisol and increased translocation of the GR complex into the nucleus (7). However, there is increasing evidence that in critically ill patients, this pathway may be impaired (3, 23, 24), but there are scattered data for the NCIN patients. The reported prevalence of adrenal insufficiency in critically ill patients varies widely (0–77%). This variation may correlate with the severity of critical illness and depends on the diagnostic criteria used. We believe that depending on the severity of illness, the critical Δ_{\max} of cortisol of $< 9 \mu\text{g/dl}$ used to define CIRCI could differ among illnesses, especially in non-critically nursed patients, and new diagnostic criteria are needed.

In the current study, all the patients with severe sepsis who recovered had Δ_{\max} of cortisol ≥ 9 $\mu\text{g}/\text{dl}$ after the standard-dose corticotrophin stimulation test in the acute phase of disease (responders). Two patients with sepsis recovered despite the fact that they had Δ_{\max} of cortisol < 9 $\mu\text{g}/\text{dl}$ after the standard-dose corticotrophin test in the acute phase of disease (non-responders) without corticosteroid treatment. This fact confirms our opinion that in NCIN patients, the degree of activation of their HPA axis and cortisol production correlates with the severity of their disease and is sufficient for their general adaptation.

We evaluated patients with sepsis and severe sepsis during the acute and recovery phases of illness. In the recovery phase, patients with sepsis had a baseline level of cortisol borderline lower and a significantly higher Δ_{\max} of cortisol after the standard-dose (250 μg) corticotrophin test than in the acute phase, which indicated that the HPA axis was recovering. Patients with severe sepsis had a significantly lower baseline cortisol but a similar Δ_{\max} of cortisol after the standard-dose (250 μg) corticotrophin test in the recovery phase as compared to the acute phase. This was probably due to the short interval between the acute and recovery phases and the inability of the HPA axis to recover or probably due to non-reproducibility of these tests during illness (25). The mechanisms that lead to alterations in the HPA axis during illness are complex and still poorly understood.

In conclusion, we believe that mild alterations in the response of the HPA axis occur in NCIN patients, but relative corticosteroid insufficiency could not be established. None of the study patients received glucocorticoid therapy, and all but three patients with severe sepsis, who were transferred to the intensive care unit and died, had a good outcome. Recommendations for the management of septic shock and ARDS with glucocorticoids have been published (7), and we agree with those. A limitation of our study is the relatively small sample size. We need further prospective controlled numerous studies to confirm the effective level of baseline and stimulated cortisol and if corticosteroid treatment is necessary in the acute phase of the disease in NCIN patients. During nursing patients with non-critical illness, physicians must be aware of clinical signs and symptoms that are suspicious for glucocorticoid insufficiency.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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