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Adrenocortical function during septic shock

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Abstract *Objective:* To investigate, in patients with severe septic shock, the adrenocortical function assessed by daily plasma cortisol determinations during the first 72 h and by the short synthetic ACTH stimulation test performed within 24 h of the onset of shock.
Design: Prospective clinical investigation.
Setting: Medical intensive care unit in a university teaching hospital.
Patients: 40 consecutive patients with documented septic shock requiring at least hemodynamic resuscitation and respiratory support.
Interventions: There were no interventions.
Measurements and results: Basal cortisol concentrations were increased with a mean value of 36.8 μg/dl (range 7.9–113). Of the overall cortisol determinations 92% were above 15 μg/dl. No statistically significant differences in basal cortisol concentrations were found when survival, type of infection, and positive blood cultures were considered. Patients with hepatic disease had significantly higher cortisol (50.1(±6.2) μg/dl versus 35.9(±3.3) μg/dl, $p = 0.035$) levels compared to other patients. No correlations were found between basal plasma cortisol concentrations and factors such as SAPS, OSF, hemodynamic measurements, duration of shock, and amount of vasopressor and/or inotropic agents. Cortisol concentrations had significant but weak correlation with ACTH levels in survivors ($r = 0.4$; $p = 0.03$; $n = 28$) but not in non-survivors ($r = 0.03$; $p = 0.85$; $n = 52$). Cortisol levels in non-survivors increased significantly from enrollment time to the 72nd hour of the survey (day 1: 38.9(±3.8) μg/dl versus day 3: 66.7(±17.1) μg/dl; $p = 0.046$) and were significantly higher than those recorded in survivors. Responses to the short ACTH stimulation test were not significantly different between survivors and non-survivors. According to the different criteria used to interpret the response to the ACTH stimulation test, incidence of adrenocortical insufficiency was highly variable ranging from 6.25–75% in patients with septic shock. Only one patient had absolute adrenocortical insufficiency (basal cortisol level below 10 μg/dl; response to the ACTH stimulation test below 18 μg/dl).
Conclusion: Our data suggest that in a selected population of patients with severe septic shock single plasma cortisol determination has no predictive value. The short ACTH stimulation test performed within the first 24 h of onset shock can neither predict outcome nor estimate impairment in adrenocortical function in patients with high basal cortisol level. Adrenal insufficiency is rare in septic shock and should

be suspected when cortisol level is below 15 μg/dl and then confirmed by a peak cortisol level lower than 18 μg/dl during the short ACTH stimulation test.

Key words Septic shock · Cortisol · ACTH · Adrenocortical insufficiency · Prognosis

Introduction

Much controversal data has been published concerning adrenocortical function during severe illness [1–4]. Patients with bacterial infection [5, 6], septic shock [4], or during other acute medical [3, 7, 8] or surgical [9] illness generally have increased plasma cortisol concentrations. Although adrenocortical insufficiency seems to be uncommon in critically ill patients [3, 8], diagnosis of hypocortisolism is vital to survival from septic insults and suggests urgent intravenous hydrocortisone therapy. However, previous studies of adrenal function using the short synthetic ACTH (corticotrophine) stimulation test in intensive care unit (ICU) patients report various incidences of adrenocortical insufficiency ranging from 0–41% [2, 4]. Adrenocortical function as a prognostic factor in ICU patients has also been suggested in recent reports [3, 8, 10], but in a well-defined population of patients with septic shock plasma cortisol concentrations were not predictive of the clinical outcome [4]. These conflicting results raise practical questions: is routine determination of serum cortisol concentration useful? Is the ACTH stimulation test in acutely ill patients like those with septic shock interpretable? In which patients with septic shock is hydrocortisone therapy indicated?

In an attempt to answer these questions we have made a prospective study of the adrenocortical function in 40 patients with septic shock within the first 72 h by using the short synthetic ACTH stimulation test and sequential determinations of plasma cortisol and ACTH concentrations.

Patients and methods

Study design

A total of 40 patients (31 men, 9 women), mean age 60.7±2.1 years (range 21–78), admitted to our medical ICU were prospectively included in this study from the moment they fulfilled the following criteria for septic shock: clinical evidence of infection, fever (>38 °C) or hypothermia (<35 °C), tachycardia (heart rate>90 beats/min), and respiratory failure (tachypnea>30/min, or hypoxia PaO_2<60 mmHg). Shock was defined as a decrease in systolic blood pressure to less than 90 mmHg, a drop of 40 mmHg from baseline values or the necessity to use vasopressor drugs to maintain systolic blood pressure, and at least one or more manifestations of inadequate organ perfusion such as acute changes in mental status, oliguria (urine output<30 ml/h for at least 1 h) or acidosis. Infections were characterized, according to cultures from blood and/or the suspected site of infection, as Gram-negative, Gram-positive, mixed Gram-positive and negative or due to non-bacterial organisms. Patients received conventional therapy including antibiotics, fluid resuscitation, vasopressor and/or inotropic agents, mechanical ventilation and haemodialysis when necessary. They underwent pulmonary arterial catheterisation with a Swan-Ganz catheter and cardiac output measurements by thermodilution twice a day during 72 h. The cardiac index (CI), systemic vascular resistance index (SVRI), and oxygen consumption (VO_2) were calculated from the variables measured using standard formulae.

Immediately after patient enrollment in the study, blood samples were obtained from the proximal channel of the Swan-Ganz catheter for determination of plasma cortisol, and adrenocorticotropic hormone (ACTH) concentrations, and then again at 8 a.m. each day until the Swan-Ganz catheter was removed. Plasma samples for cortisol and ACTH were analysed by radioimmunoassay. Normal values of cortisol were: 15–25 μg/dl and ACTH: 18–58 ng/l.

A short ACTH stimulation test (Synacthene, Ciba-Geigy, Rueil-Malmaison, France) was done within 24 h of the onset of shock with 0.25 mg tetracosactin given intravenously. The ACTH stimulation test was considered valid if the hemodynamic status, ventilator settings and fluid infusion rates were kept constant during the test, and if no new medication was administered. Blood samples were taken immediately before the test (T0) and 60 min afterwards (T60). Because of many possible interpretations of the short ACTH stimulation test, results were analysed using different criteria: absolute rise in cortisol levels over baseline (T60-T0) [2]; ratio of basal and stimulated cortisol (T0/T60) [11]; rise in plasma cortisol of at least 7 μg/dl (T60-T0≥7 μg/dl) [10]; rise in plasma cortisol of at least 9 μg/dl (T60-T0≥9 μg/dl) [2]; stimulated cortisol level over 18 μg/dl (T60>18 μg/dl) [3]. Patients with hormonal diseases and/or those receiving corticosteroids or medications known to interfere with hormonal responses to stress were excluded. Normals for comparison consisted of 20 patients on a general medicine service, without any clinical or laboratory evidence of adrenocortical disorder.

Severity of illness at the time of patient enrollment was assessed using the Simplified Acute Physiology Score (SAPS) for ICU patients [12], and the number of acute Organ System Failure (OSF) as defined by Knaus et al. [13]. Survival was defined as survival to ICU discharge.

Statistical analysis

Descriptive statistics are reported as mean±SEM. The Mann-Whitney U test was used to compare patients data between survivors and non-survivors. Correlations were calculated using regression analysis. Comparisons of categorical data were made using the chi-squared test. For all comparisons and correlations, differences were considered significant when $p<0.05$. All calculations were done using the Statview II software package (Abacus Concepts, Inc, Berkeley, CA). For technical or practical reasons, blood samples could not be obtained from each patient at all time points. The number of patients "*n*" is indicated on the figures and tables for each group and time point.

Table 1 Clinical and biochemical data at enrollment time for 40 patients. (*PAWP* pulmonary artery wedge pressue, *CI* cardiac index, *MAP* mean arterial pressure, *SVRI* systemic vascular resistance index, VO_2 oxygen consumption)

	Entire group ($n = 40$)	Survivors ($n = 11$)	Non-survivors ($n = 29$)	p-value
SAPS	21.2 (±0.7)	22.1 (±1)	20.9 (±0.9)	0.31
OSF	3.8 (±0.2)	3.4 (±0.5)	4 (±0.2)	0.13
Type of infection				
Gram-positive	13	6	7	
Gram-negative	15	1	14	0.016
Hours in shock	21.2 (±4.3)	14.7 (±3.2)	23.6 (±5.8)	0.59
PAWP (mmHg)	13.8 (±0.8)	12.4 (±0.8)	14.3 (±1)	0.09
CI (l/min/m^2)	4.8 (±0.3)	4.7 (±0.4)	4.9 (±0.4)	0.59
MAP (mmHg)	72 (±2.2)	69.7 (±2.9)	72.9 (±2.8)	0.53
SVRI (IU)	14.8 (±1.4)	14.3 (±2.4)	15 (±1.8)	0.74
VO_2 (ml/min/m^2)	188.4 (±16.5)	166.8 (±14.9)	194.1 (±20.5)	0.59
Cortisol (μg/dl)	36.8 (±3.1)	31.1 (±4.5)	38.9 (±3.80)	0.23
ACTH (ng/l)	56 (±7.7)	50.2 (±13.4)	58.3 (±9.5)	0.65

Results

Patients

Some characteristics of the patients in this study are given in Table 1. No significant differences were found considering the mean Simplified Acute Physiology Score, number of acute Organ System Failures, hours in shock, and hemodynamic measurements, between survivors ($n = 11$; 27.5%) and non-survivors ($n = 29$; 72.5%). Patients with Gram-negative-related septic shock were less likely to survive than patients with Gram-positive or other etiologies despite the similar distribution of underlying disease and severity of shock. Survivors had a significantly higher ICU stay (59.7(±8.1) days versus 13.8(±2.9) days; $p = 0.0001$) when compared to non-survivors.

Basal cortisol and ACTH concentrations

Basal plasma cortisol concentrations were increased in patients with septic shock with a mean value of 36.8(±3.1) μg/dl (range: 7.9–113). The mean basal ACTH level was normal: 56(±7.7) ng/l (range: 13–192). Basal cortisol levels were above 10 μg/dl in all but one patient who died. For the overall samples, 92% of the cortisol determinations were above 15 μg/dl, and 3 patients, all survivors, had at least one cortisol value between 10 μg/dl and 15 μg/dl. There were no statistically significant differences in basal cortisol concentrations when survival, type of infection, and positive blood cultures were considered. Patients with hepatic disease had significantly higher cortisol (50.1(±6.2) μg/dl versus 35.9(±3.3) μg/dl, $p = 0.035$) levels compared to other patients.

Cortisol and clinical or biochemical data correlations

The correlations between basal plasma cortisol concentrations and factors such as SAPS, OSF, mean arterial pressure, CI, SVRI, VO_2, duration of shock before collection of the blood sample, and amount of vasopressor and/or inotropic agents are shown in Table 2. The cortisol concentrations were significantly (although weakly= correlated with ACTH levels in survivors ($r = 0.4$; $p = 0.03$; $n = 28$) but not in non-survivors ($r = 0.03$; $p = 0.85$; $n = 52$).

Changes in cortisol and ACTH concentrations

As illustrated in Fig. 1 and mentioned in Table 1, at enrollment time the average plasma cortisol concentrations in non-survivors were not significantly different from those in survivors. At any time during the first 72 h following enrollment the cortisol concentrations were significantly higher in non-survivors than those recorded in survivors Cortisol levels increased significantly in non-survivors from enrollment time to the 72nd hour of the survey (day 1: 38.9(±3.8) μg/dl versus day 3: 66.7(±17.1) μg/dl; $p = 0.046$).

Table 2 Correlation coefficients and significance levels for association between basal plasma cortisol concentrations ($n = 40$) and clinical variables

	r Value	p Value
SAPS	0.12	0.46
OSF	0.13	0.41
MAP (mmHg)	0.05	0.74
CI (l/min/m^2)	0.28	0.08
SVRI (IU)	0.13	0.43
VO_2 (ml/min/m^2)	0.03	0.89
Hours in shock	0.002	0.99
Vasopressor and/or inotropic agents	0.07	0.66

Table 3 Cortisol response afer 0.25 mg intravenous injection of synthetic ACTH in normal subjects and patients with septic shock. (*T0* basal cortisol level, *T60* 60 min cortisol level, *p* value survivors versus non-survivors)

	Normal subjects ($n = 20$)	Entire group ($n = 32$)	Survivors ($n = 11$)	Non-survivors ($n = 21$)	p Value
T0 (μg/dl)	13.7 (±6.4)	37.2 (±4.6)	30 (±4.3)	40.9 (±6.5)	0.36
T60 (μg/dl)	27.9 (±6.9)	43.6 (±4.9)	38.4 (±4.4)	46.4 (±7)	0.77
T60-T0 (μg/dl)	14.3 (±4)	6.2 (±1.2)	8.4 (±2.2)	5.5 (±1.4)	0.27
T0/T60	0.5 (±0.1)	0.84 (±0.03)	0.77 (±0.06)	0.88 (±0.03)	0.15
T60-T0 ≥ 7 μg/dl	20	10	4	6	0.58
T60-T0 ≥ 9 μg/dl	16	8	3	5	0.77
T60 > 18 μg/dl	20	30	10	20	0.63

There were no statistically significant changes in ACTH concentrations at any time during the 72 h of the survey and between survivors and non-survivors.

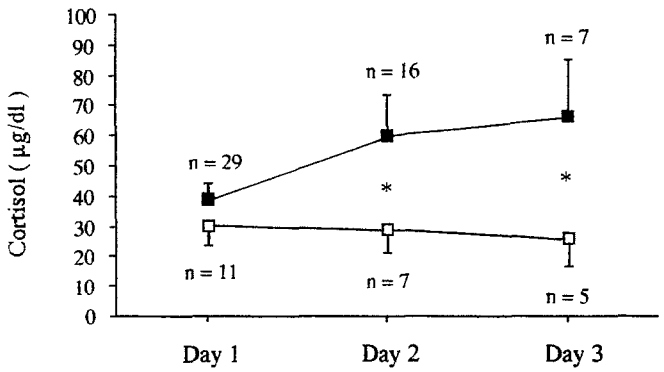

Fig. 1 Daily changes in plasma cortisol concentrations in patients with septic shock. Data are mean±SED. * $p < 0.05$ for the difference between survivors (□) and non-survivors (■). Plasma cortisol concentrations increased significantly from day 1 to day 3 in non-survivors ($p < 0.05$)

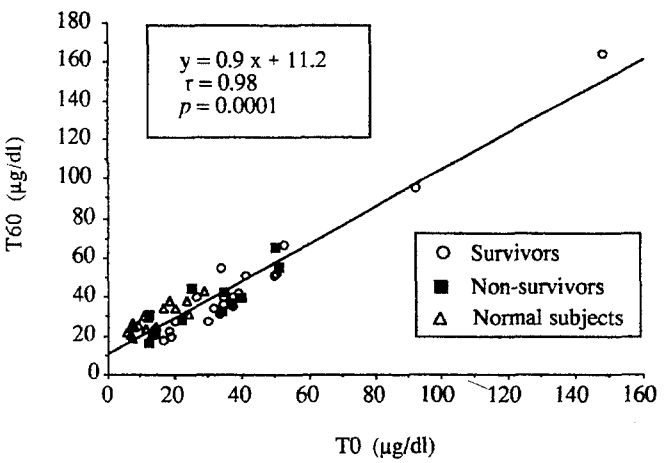

Fig. 2 Scattergram of the correlation between basal cortisol levels (*T0*) and 60 min cortisol levels (*T60*) after 0.25 mg intravenous injection of synthetic ACTH in 20 normal subjects and 32 patients with septic shock

ACTH stimulation test

Responses of the short test of adrenocortical function in normal subjects were comparable to the results obtained in other studies [14, 15]. As shown in Table 3, whatever the criteria used, responses to the short ACTH stimulation test were not significantly different between survivors and non-survivors. Patients with a poor response to synthetic ACTH (T60-T0 ≤ 7 μg/dl or T60-T0 < 9 μg/dl) did not have a significantly different mean basal cortisol or basal ACTH concentrations compared to those with an adequate response. According to the different criteria used for the ACTH stimulation test, incidence of adrenocortical insufficiency was variable: 6.25% for T60 ≤ 18 μg/dl to 75% for T60-T0 ≤ 9 μg/dl. The 3 patients with basal cortisol value between 10 μg/dl and 15 μg/dl had a stimulated cortisol level above 18 μg/dl. Cortisol response to synthetic ACTH correlated positively with basal cortisol in normal subjects ($r = 0.8$; $p = 0.0001$; $n = 20$), survivors ($r = 0.87$; $p = 0.0006$; $n = 11$) and non-survivors ($r = 0.98$; $p = 0.0001$; $n = 21$) (Fig. 2).

Discussion

In this study on patients with severe septic shock, it was found that a single plasma cortisol determination has no predictive value. The short ACTH stimulation test performed within the first 24 h of onset of shock can neither predict outcome nor estimate impairment in adrenocortical function in patients with high basal cortisol level. However during the first 72 h, serial morning determination in non-survivor patients showed a rise in plasma cortisol levels compared to survivor patients.

The usual finding in critically ill patients requiring intensive therapy is an increase in cortisol secretion with consistently raised serum levels [1–4, 7, 8]. However cortisol values during septic shock range from normal to 20 times the high normal value [4]. This discrepancy may have several explanations: disruption of the circadian rhythm of cortisol in severely stressed patients [16, 17]; reduced cortisol half-life [18]; depletion of steroid binding globulin [19]; decreased rate of blood cortisol extraction [18]; impairment of the hypothalamic-pituitary-adrenal axis [20, 21]; or reduced heptic degradation [22]. In our

study patients with hepatic failure had higher cortisol concentrations. All these factors may lead to the wide variation in measured adrenocortical response to severe septic shock. Thus, it is difficult to deduce appropriate cortisol levels in patients with severe sepsis. In our study, 92 per cent of the patients had values higher than 15 μg/dl which may be considered as the minimum useful level for these critically ill patients [9]. Cortisol concentrations between 10 and 15 μg/dl seem to be still adequate since all of our patients with these concentrations survived. However adrenocortical insufficiency should be reasonably suspected when cortisol level is below 15 μg/dl during septic shock [4], and then confirmed by a peak cortisol level lower than 18 μg/dl during the short ACTH stimulation test [3, 23].

Single plasma cortisol determinations have been correlated with severity of illness and mortality in a large population of ICU patients [3, 8, 24]. Patients with high cortisol levels are likely to have a poor prognosis. But our data, similar to that of Schein et al. [4], also demonstrated that a single point cortisol determination on the onset of shock in a defined population of patients with severe septic shock is not correlated with outcome. Likewise cortisol concentrations were not correlated with severity of illness appreciated by SAPS, OSF, hemodynamic measurements, doses of vasopressors and/or inotropic agents and time from onset of shock to measurement. However we find that repeated determinations showing an increase in mean plasma cortisol levels indicate poor survival in these patients. A similar pattern has been observed by other investigators in patients with septic shock [25] or chronic severe illness [8]. On the other hand, Finlay et al. [1] reported increased mortality when morning cortisol levels showed a progressive fall to less than 12 μg/dl, which is in contradiction with high cortisol concentrations observed in the preterminal state [6, 18, 26].

Under normal physiologic conditions the adrenocorticotropic hormone stimulates the secretion of glucocorticoid hormones which by feedback inhibition regulate both the corticotropin-releasing factor and adrenocorticotropic hormone secretions. A relationship between plasma cortisol and ACTH concentrations has been reported in patients with septic shock [21] or accidental injury [20]. In our study ACTH was found to be in significant correlation with cortisol solely in survivors. This result suggests an impairment in the hypothalamic-pituitary-adrenal axis in non-survivors due to other factors influencing the adrenocortical response such as cytokines [27], tumor necrosis factor [28], prostacyclin [29] or decreased adrenal bloodflow [30].

Incidence of adrenal insufficiency in ICU patients seems to be highly variable in the literature [2, 3, 8, 10, 11, 24]. These conflicting results are explained by the different criteria used to interpret the short ACTH stimulation test. In our study 6.5–75% of the patients may be considered to suffer from adrenal insufficiency. In our view absolute adrenal insufficiency exists when the cortisol concentration is below 15 μg/dl and confirmed by a 60 min stimulated cortisol assay, after 0.25 mg of synthetic ACTH given intravenously, with a value less than 18 μg/dl. This diagnosis suggest urgent substitutive hydrocortisone therapy. Only one of our 40 patients had these two criteria. This indicates that absolute adrenal insufficiency is uncommon in selected critically ill patients [3, 4, 8], thus systematic determination of serum cortisol concentration during septic shock is not mandatory. However adrenal insufficiency should be suspected in patients with severe sepsis where there is the slightest doubt with regard to situations favouring the occurrence of adrenal lesions such as bleeding disorders or anticoagulant therapy, purpura fulminans, thermal injury, postoperative period, administration of ketoconazole or etomidate, or chronic glucocorticoid therapy.

The notion of absolute adrenal insufficiency is gradually being replaced by the idea of relative adrenal insufficiency [2, 6, 10]. Relative adrenal insufficiency has been determined by a poor response to corticotropin, even in patients with high cortisol concentrations, and associated with increased mortality. In a prospective study [10] hydrocortisone replacement reduced mortality in a limited population of severely stressed patients with relative adrenal insufficiency. In our study, results of the short ACTH stimulation test neither predict outcome, nor detect patients requiring hydrocortisone therapy. It is conceivable that the stimulation from the already maximally stimulated adrenal gland may result in a blunted response to synthetic ACTH. Thus the ACTH stimulation test seems of poor value for the majority of the patients during the first 24 h of septic shock.

Controlled clinical trials of early-high-dose corticosteroids showed no improvement in the prevention of shock in established sepsis, nor in shock reversal if it had already occurred, nor in mortality [31–33]. However in late septic shock, hemodynamic improvement with physiological doses of hydrocortisone have been reported in some cases [34, 35], possibly related to an increase of vascular responsiveness to catecholamines. These results have to be confirmed by prospective double-blind randomized studies. Improvement of outcome, with the systematic use of physiological doses of glucocorticoids during septic shock, remains to be proved.

In conclusion, our data suggest that systematic plasma cortisol level determination during septic shock is not necessary, apart from situations at risk of adrenal lesions. Hydrocortisone therapy for adrenal insufficiency must be started in the setting of septic shock when the cortisol level is below 15 μg/dl, and when the peak cortisol level in response to the short ACTH stimulation test is lower than 18 μg/dl. Initial cortisol concentration and response to the ACTH stimulation test have no predictive value, however cortisol levels increase significantly in non-survivors patients during the first 72 h of septic shock.

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