

Daniele Dalegrave¹, Rafael Lockshin Silva¹,
Macon Becker¹, Lísia Varella Gehrke¹, Gilberto
Friedman^{1,2}

Relative adrenal insufficiency as a predictor of disease severity and mortality in severe septic shock

Insuficiência adrenal relativa como preditora de gravidade de doença e mortalidade do choque séptico

1. Central Intensive Care Unit, Complexo Hospitalar Santa Casa - Porto Alegre (RS), Brazil.
2. Universidade Federal do Rio Grande do Sul - UFRGS - Porto Alegre (RS), Brazil.

ABSTRACT

Objective: To evaluate if cortisol responses to 250 µg of intravenously administered adrenocorticotropic hormone are related to disease severity and, hence, mortality.

Methods: This is a retrospective study in a medical-surgical intensive care unit of a university hospital. We studied 69 consecutive patients with septic shock over a 1-yr period; these patients underwent a short 250-µg adrenocorticotropic hormone test because they exhibited >6 hours of progressive hemodynamic instability requiring repeated fluid challenges and vasopressor treatment to maintain blood pressure. The test was performed by intravenously injecting 250 µg of synthetic adrenocorticotropic hormone and measuring cortisol immediately before injection, 30 minutes post-injection and 60 minutes post-injection.

Results: The mean APACHE II score was 22±7. The intensive care unit mortality rate at day 28 was 55%. Median baseline cortisol levels (19 [11-27] µg/dL *versus* 24 [18-34] µg/dL,

p=0.047) and median baseline cortisol/albumin ratios (7.6 [4.6-12.3] *versus* 13.9 [8.8-18.5]; p=0.01) were lower in survivors than in non-survivors. Responders and non-responders had similar baseline clinical data and outcomes. The variables that were significantly correlated with outcome based on the area under the ROC curves (AUC) were APACHE II (AUC=0.67 [0.535 to 0.781]), baseline cortisol (µg/dl) (AUC=0.662 [0.536 to 0.773]), peak cortisol (µg/dl) (AUC=0.642 [0.515 to 0.755]) and baseline cortisol/albumin (AUC=0.75 [0.621 to 0.849]).

Conclusions: Increased basal cortisol is associated with mortality and disease severity. Cortisol responses upon adrenocorticotropic hormone stimulation were not related to outcome. The cortisol/albumin ratio does not predict unfavorable outcomes better than total cortisol levels or help to improve the accuracy of the adrenocorticotropic hormone test.

Keywords: Adrenal insufficiency; Critical illness; Adrenocorticotropic hormone/administration & dosage; Hydrocortisone; Shock, septic

This study was conducted at Central Intensive Care Unit, Complexo Hospitalar Santa Casa - Porto Alegre (RS), Brazil.

Conflicts of interest: None.

Submitted on June 6, 2012
Accepted on December 4, 2012

Corresponding author:

Gilberto Friedman
UTI Central, Complexo Hospitalar Santa Casa
Rua Professor Annes Dias, 295 - Centro
Zip Code: 90.020-090- Porto Alegre(RS), Brazil
E-mail: gfriedman@hcpa.ufrgs.br

INTRODUCTION

Activation of the hypothalamic-pituitary-adrenal axis (HPA) is an important hormonal response to disease and serves to adapt the organism to physiologic stress.^(1,2) Blunted adrenal corticosteroid production during critical illness, particularly septic shock, has been termed relative adrenal insufficiency (RAI) or critical illness-related corticosteroid insufficiency (CIRCI). During CIRCI, cortisol serum levels are considered insufficient for the degree of stress (even when supranormal), as manifested by a poor response to additional stimuli.^(3,4) In the absence of structural defects,

CIRCI could indicate transiently diminished adrenal reserve. The standard test to evaluate adrenocortical function is intravenous administration of 250 µg of adrenocorticotrophic hormone (ACTH). Relatively high circulating cortisol levels combined with a diminished increase after ACTH administration may be associated with severe disease and high mortality.⁽⁴⁻¹⁵⁾ However, it is unknown whether ACTH-cortisol responses in severe sepsis and septic shock are caused by or contribute to critical illness and, thus, have a marker or mediator role in regard to mortality.⁽²⁾

The use of adrenocortical stimulation tests in patients with septic shock remains controversial. Metyrapone and insulin tolerance tests are considered more accurate for the diagnosis of adrenal failure. Unfortunately, both are hardly feasible in critically ill patients.^(2,16,17) Baseline cortisol levels alone could also be used to help identify CIRCI; however, no trials could identify a baseline cortisol cutoff point that could be used to diagnose CIRCI or guide therapy.^(2,18,19) In the course of severe disease, low levels of cortisol-binding proteins and hypoalbuminemia may lower total cortisol levels and responses to ACTH independently of free cortisol levels and in the absence of CIRCI.⁽²⁰⁻²²⁾ However, the measurement of free cortisol (biologically active) in serum or saliva is not widely available and requires further studies in critical care patients.^(2,13) Instead, the cortisol/albumin ratio has been used to estimate free cortisol because albumin binds cortisol, although to a lesser extent than cortisol-binding globulin (CBG). Both albumin and CBG levels may decrease to the same extent in critical illness.^(15,20-23) Due to the difficult application or low accuracy of the tests, the stimulation test with a high dose of cosyntropin (250 µg) is a standard test for CIRCI. Several investigators have shown that a failure of the post-stimulation plasma cortisol levels to increase to at least 9 µg/dL could indicate survivors and non-survivors of septic shock.⁽⁵⁾ Some experts criticize this test with regard to the diagnosis of CIRCI, arguing that the high dose of cosyntropin is many times above the serum levels of ACTH present in septic shock patients, leading to diagnostic criteria with high specificity but low sensitivity.^(14,24)

Nevertheless, in several studies, hydrocortisone substitution therapy may have had beneficial effects on the hemodynamics and outcome of patients with severe septic shock needing vasopressor/inotropic treatment, particularly when associated with a diminished ACTH response.^(7-9,11,19,24-27) However, this

finding is still controversial, especially in the aftermath of the publication of the CORTICUS study, which raised doubts about the utility of the ACTH test and even the beneficial effect of low-dose hydrocortisone in severe sepsis.⁽²⁸⁾ Although CIRCI is recognized as a dysfunction,^(5,15) different trials have shown different results about the treatment of this dysfunction.^(26,28) One explanation for the heterogeneous results of cortisol supplementation concerns the definition of CIRCI.

First, to evaluate the concept of CIRCI, we hypothesized that cortisol responses to ACTH are related to the disease severity and, hence, mortality. Next, we evaluated whether the cortisol levels related to albumin levels could be used to estimate free cortisol and better address the relationship between CIRCI and morbidity and mortality. Therefore, a retrospective cohort study was undertaken in 69 consecutive patients with septic shock who underwent an ACTH test in our intensive care unit (ICU).

METHODS

Study population and ACTH test

This study was approved by the Research Ethics Committee of the Complexo Hospitalar Santa Casa. Informed consent was waived because the ACTH test was performed on clinical grounds, rather than on investigational grounds. The medical records of all consecutive patients admitted to the 18-bed ICU of a university hospital (Complexo Hospitalar Santa Casa) over a 1-year period (May 2005-May 2006) who had septic shock, underwent a short ACTH (Ciba, France) stimulation test, and had baseline cortisol values at 30- and 60-min after 250 µg of intravenous ACTH were reviewed. Sepsis at the ACTH test day was defined as the presence of systemic inflammatory response syndrome with a suspected or proven infection.⁽²⁹⁾ Systemic inflammatory response syndrome was defined as two or more of the following criteria: temperature >38°C or <35.5°C, leukocyte count >12 or <4 X 10⁹/L, heart rate >90 beats/min, and respiratory rate >20 breaths/min or the presence of mechanical ventilation. The patients were classified as having septic shock when their systolic blood pressure was <90 mmHg or their mean arterial pressure was <60 mm Hg, requiring repeated fluid challenges and vasopressor treatment. The exclusion criteria were incomplete medical records, known abnormalities of the HPA axis, or chronic use of corticosteroids and corticosteroids indicated for other medical reasons (i.e., severe bronchospasm).

The ACTH test was performed in any patient suspected of having some degree of adrenocortical dysfunction based on >6 hours of hemodynamic instability requiring repeated fluid challenges and vasopressor treatment to maintain a minimal blood pressure. Blood samples for serum cortisol measurements were taken immediately before (T=0) and at T=30 and T=60 minutes after intravenous injection of ACTH. The highest values at T=30 and T=60 minutes were used to indicate the peak response, and the increase in these values relative to baseline values were calculated. We determined the absolute and proportional changes (Δ %) between the baseline cortisol levels and the peak responses to ACTH. Cortisol was measured by chemiluminescence (ADVIA Centaur System, Bayer Healthcare LLC, Tarrytown, NY, USA).

Hydrocortisone administration (starting at 50 mg intravenously, every 6 hours) was initiated by the attending intensivist while awaiting the ACTH test results. If the test was considered normal, hydrocortisone was discontinued. No patients were treated with ketoconazole or etomidate for intubation. All patients were treated for a maximum of 7 days.

Data collection

General characteristics, including age, gender, type and reason of admission, and underlying diseases, were recorded. Cortisol/albumin ratios were calculated as an indicator of free cortisol. Disease severity was assessed by calculating the Acute Physiology and Chronic Health Evaluation II (APACHE II) at admission.⁽³⁰⁾ After the day of testing, the following data were recorded: start and duration of treatment with hydrocortisone, outcome in the ICU, length of ICU stay, and hospital mortality.

Statistical analysis

For normally distributed parameters, Student's *t*-test was used to compare the means of different groups. The Mann-Whitney test was used for nonparametric testing between groups. Fisher's exact test was used to analyze differences in proportions between groups. The Spearman correlation coefficient was calculated to express relations between variables. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive value of the cortisol levels for the outcome and identify the levels with the highest sensitivity and specificity. Data are expressed as the mean \pm standard deviation, as the median (25-75 percentiles), or as percentages. A two-sided $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Sixty-nine patients were included. The mean APACHE II score was 22 ± 7 . The overall ICU mortality rate at day 28 was 55%, and hospital mortality was 72%. The median(range) of ICU stay was 15 (1-122) days, and the median(range) of hospital stay was 19 (1-156) days. The most frequent underlying disease categories were cardiovascular (31%; $n=22$), renal (18%; $n=13$), pulmonary (24%; $n=16$) and gastrointestinal (26%; $n=18$).

Table 1 shows the clinical characteristics of survivors and non-survivors. Baseline cortisol levels and ACTH responses were highly heterogeneous, in both survivors and in non-survivors, while albumin levels, which were available in 91% of patients, did not differ among the outcome groups. The survivors had baseline cortisol levels and baseline cortisol/albumin ratios lower than those of the non-survivors. Forty patients (58%) had a low baseline cortisol level ($<25 \mu\text{g/dL}$), and of these patients, 12 (30%) were survivors. Both survivors and non-survivors had similar peak and cortisol increase levels. Relative cortisol increase was similar in survivors and non-survivors ($p=0.246$). In non-survivors ACTH testing

Table 1 - Characteristics of survivors and non-survivors at day 28

	Survivors (N=19)	Non-survivors (N=50)	p value
Age (years)	57 [32-72]	68 [53-75]	0.01
Responders/non-responders	9/9	30/20	0.58
Albumin (g/L)	2.2 ± 0.5	1.9 ± 0.7	0.11
Baseline cortisol ($\mu\text{g/dL}$)	19 [11-27]	24 [18-34]	0.047
Baseline cortisol $< 25 \mu\text{g/dL}$	12 (63)	28(56)	0.785
Baseline cortisol/albumin	7.6 [4.6-12.3]	13.9 [8.8-18.5]	0.003
Peak cortisol ($\mu\text{g/dL}$)	$35.6 [17.9-42.9]$	$40.6 [30.1-48.2]$	0.068
Cortisol increase ($\mu\text{g/dL}$)	12.4 ± 8.6	14.6 ± 12.3	0.486
Cortisol increase/albumin	5.2 [3.6-8.1]	6.7 [3.0-11.9]	0.35
Cortisol increase (%)	$72.7 [24.0-131.9]$	$45.3 [20.7-94.7]$	0.246
Days from admission to test	1.5 [0-2]	2 [1-4]	0.01
Type of admission			
Surgical	5 (26)	17 (34)	
Medical	14 (74)	33 (66)	
Location of infection			
Pulmonary	10 (53)	25 (50)	
Abdomen	7 (37)	13 (26)	
Soft tissue	1 (5)	6 (12)	
Other	1 (5)	6 (12)	
Admission APACHE II	18 ± 7	23 ± 7	0.05
ICU stay (days)	11 [11-19]	19 [10-33]	0.23
Hospital stay (days)	24 [16-27]	19 [10-35]	0.46

APACHE - Acute Physiology and Chronic Health evaluation; ICU - intensive care unit. Data are expressed as the mean \pm standard deviation, median [percentiles 25-75%] or number (%), where appropriate, by the indicated statistical test.

Table 2 - Clinical data about the responders and non-responders to the adrenocorticotrophic hormone test

	Responders (N=40)	Nonresponders (N=29)	p value
Survivor/non-survivor	10/30	9/20	0.58
Age (years)	60.7 ± 17.7	62.2 ± 16.2	0.73
Albumin (g/L)	2.2 [1.6-2.3]	1.8 [1.6-2.1]	0.143
Baseline cortisol (µg/dL)	22.8 [17.0-31.4]	26.6 [12.9-34.5]	0.857
Baseline cortisol < 25 µg/dL	27 (68)	13 (45)	0.084
Baseline cortisol/albumin	11.0 [6.9-15.8]	14.0 [5.4-18.8]	0.566
Peak cortisol (µg/dL)	43.2 [33.8-53.5]	30.4 [17.9-41.1]	<0.001
Cortisol increase (µg/dL)	17.8 [13.6-23.4]	4.5 [3.0-7.1]	<0.001
Cortisol increase/albumin	8.1 [6.7-14.2]	2.6 [1.3-4.0]	<0.001
Cortisol increase (%)	78.6 [53.3-123.5]	19.9 [8.8-34.7]	<0.001
Admission APACHE II	21.5 ± 7.6	22.0 ± 7.8	0.825

APACHE - Acute Physiology and Chronic Health evaluation. Data are expressed as the mean ± standard deviation, median [percentiles 25-75%] or number (%), where appropriate, by the indicated statistical test.

was performed a few days later after admission than in survivors because non-survivors had a higher frequency of ICU-acquired sepsis. The APACHE II score on admission was higher in non-survivors than in survivors.

Table 2 shows clinical data based on the ACTH test. The mortality rate among non-responders and responders was similar (69% versus 75%, $p=0.58$). Albumin levels, baseline cortisol levels and cortisol/albumin ratios were similar in responders and non-responders. By definition, all variables related to the ACTH response were significantly different. Six patients showed very low basal cortisol levels (≤ 10 µg/dL), and 3 of these were responders.

Cortisol levels and ACTH test responses among hypoalbuminemic and normoalbuminemic patients were similar (Table 3). Albumin levels did not correlate with the baseline levels ($r=-0.01$), peak cortisol levels ($r=0.08$) or increases in cortisol ($r=0.13$). There was an excellent correlation between total baseline cortisol values and

Table 3 - Clinical data about hypoalbuminemics and normoalbuminemics

	Hypoalbuminemics (N=50)	Normoalbuminemics (N=12)	p value
Survivor/non-survivor	10/40	5/7	0.142
Age (years)	63 ± 16	62 ± 19	0.064
Albumin (g/L)	1.8 ± 0.4	3.0 ± 0.4	<0.001
Baseline cortisol (µg/dL)	23 [15-32]	22 [15-33]	0.866
Baseline cortisol < 25 µg/dL	30 (60)	9 (75)	0.508
Baseline cortisol/albumin	13.3 [7.3-18.4]	7.8 [4.8-10.2]	0.011
Peak cortisol (µg/dL)	40 ± 21	36 ± 12	0.538
Cortisol increase (µg/dL)	14 ± 13	13 ± 7	0.781
Cortisol increase/albumin	8.2 ± 6.9	4.7 ± 2.5	0.08
Cortisol increase (%)	0.57 ± 0.21	0.63 ± 0.32	0.964
Admission APACHE II	22.3 ± 7.8	21.4 ± 6.8	0.754

APACHE - Acute Physiology and Chronic Health Evaluation. Hypoalbuminemia; albuminemia level < 2.5 mg/dL. Data are expressed as the mean ± standard deviation, median [percentiles 25-75%] or number (%), where appropriate, by the indicated statistical test.

cortisol/albumin values ($r=0.86$, $p<0.0001$). Baseline cortisol values correlated with peak values and peak cortisol/albumin values and inversely correlated with relative increases in cortisol levels (Figure 1). Baseline cortisol level and cortisol/albumin ratios correlated weakly with APACHE II score ($r=0.32$ and $r=0.39$, $p<0.01$ and $p<0.001$, respectively).

Receiver operating characteristic curves are shown in figure 2. The baseline cortisol level with the greatest discriminative value for outcome in the receiver operating characteristic curve was 16.5 µg/dL, which had a sensitivity (prediction of mortality) of 50% and a specificity (prediction of survival) of 80% (ROC area 0.662 [0.536 to 0.773], $p=0.02$). Similarly, the peak

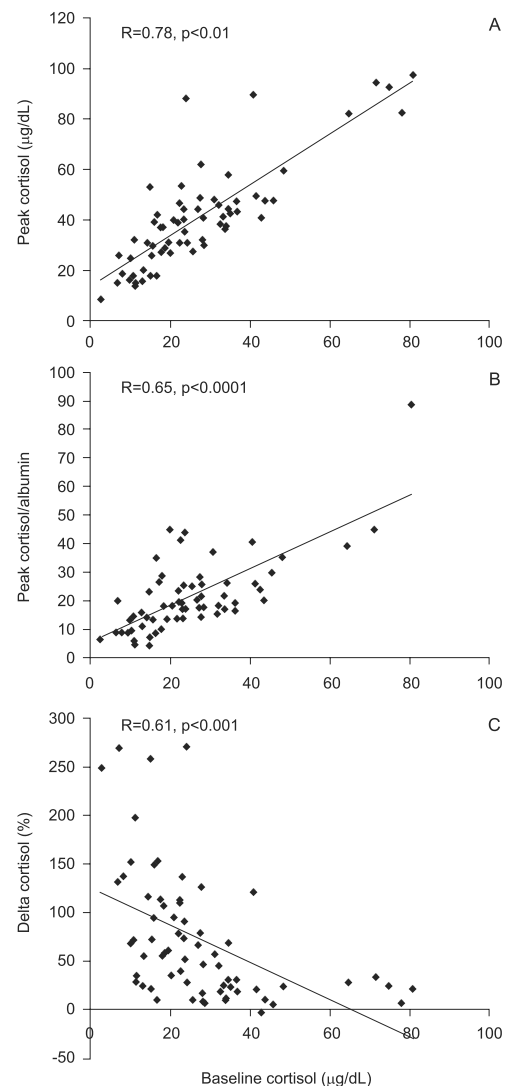


Figure 1 - Correlations between baseline total blood cortisol and (A) peak blood cortisol, (B) blood cortisol/albumin ratio and (C) percent change of the blood cortisol (delta cortisol=peak cortisol/baseline cortisol). R - Spearman correlation.

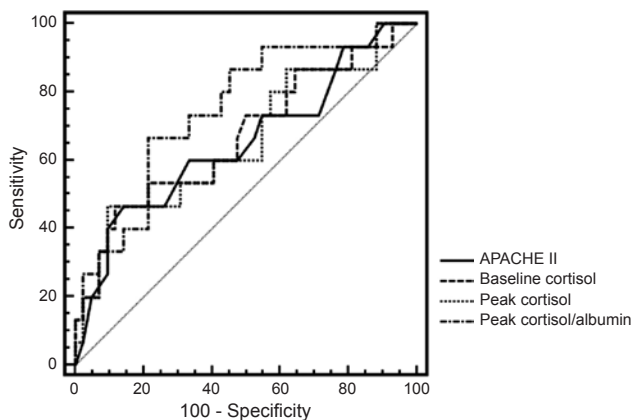


Figure 2 - Receiver operating characteristic curves regarding APACHE II, baseline total blood cortisol, peak blood cortisol and baseline total blood cortisol/albumin ratio. The area under the curve for APACHE II is 0.67 [0.535 to 0.781], baseline cortisol is 0.662 [0.536 to 0.773], peak cortisol is 0.642 [0.515 to 0.755] and baseline cortisol/albumin is 0.75 [0.621 to 0.849].

cortisol level that best discriminated outcome was 20.3 $\mu\text{g/dL}$, which had a sensitivity of 39% and a specificity of 92% (ROC area 0.642 [0.515 to 0.755], $p=0.05$). A baseline cortisol/albumin ratio of 13.3 had a sensitivity of 88% and a specificity of 56% (ROC area 0.75 [0.621 to 0.849], $p=0.0001$). The other ACTH-cortisol related variables did not predict outcome. An APACHE II score of 16 had a sensitivity of 50% and a specificity of 85% (ROC area 0.67 [0.535 to 0.781], $p=0.025$).

DISCUSSION

The present study highlights several findings. High unstimulated cortisol, particularly when related to albumin, was associated with disease severity and mortality. However, the ACTH-cortisol responses were not clearly associated with outcome.

Our data agree with those in the literature concerning the high mortality rate among septic shock patients. Although the 55% overall ICU mortality (at day 28) may be relatively high, this value is in accordance with the high mortality rates found among different epidemiological Brazilian studies on septic shock and can also be explained by the relatively high disease severities.^(31,32)

The literature is highly heterogeneous regarding the cortisol cutoff values used to define abnormal cortisol/ACTH responses and regarding the critically ill patient population studied. Cutoff baseline values range between 15 and 60 $\mu\text{g/dL}$ and ACTH-induced increases range from 9 to 15 $\mu\text{g/dL}$; below these values, cortisol levels were suggested to be associated with morbidity and mortality.^(1,4,5,7-9,11,13,14,17,24,27) Like other

studies, the outcome groups in our study differed with respect to baseline cortisol levels, which were correlated with disease severity scores.^(4-6,11,13;20,25,26) However, in our study, differences upon ACTH administration, even when corrected to albumin levels, were not observed in non-survivors. Because ACTH-cortisol responses did not predict outcome independently of disease severity, a low cortisol response to ACTH may be a marker rather than a mediator of severe disease and associated mortality.^(2,28) This result suggests that abnormal cortisol levels lack attributable mortality but may be a sign of severe disease. Although the overall disease severity and mortality were similar in our study and that of Annane et al.,⁽²⁶⁾ our findings are in contrast to the results of that study and those of other reports, which demonstrated that increased cortisol values contributed to mortality prediction independently of disease severity.^(5,24,33) We found that responder patients who had their corticosteroid infusion stopped early and non-responder patients who had a continuous corticosteroid infusion for 7 days had very similar clinical outcomes and mortality. This finding contributes to the idea that neither absolute cortisol levels or in response to the ACTH test should guide corticosteroid treatment. This result is also in accordance with those of other studies dissociating CIRCI from an adverse outcome.^(28,34) Perhaps refractory septic shock could be the only indication for corticosteroids treatment as usually done in most centers nowadays and is recommended in the Surviving Sepsis Campaign (SSC) guidelines.^(35,36)

The debate regarding the usefulness of total cortisol measurements without an ACTH stimulation test continues.^(2,14,15,17,18,22,28,37) There are numerous definitions for possible adrenal insufficiency based on random serum cortisol measurements. In our study, the proportion of patients with adrenal insufficiency varied from 9% (cortisol levels ≤ 10 $\mu\text{g/dL}$) to 58% (cortisol levels < 25 $\mu\text{g/dL}$). If very low cortisol levels indicate absolute adrenal insufficiency, the ACTH test would be dispensable. However, ACTH tests revealed that half of the patients were responders. By examining patients with low cortisol levels (< 25 $\mu\text{g/dL}$), we were unable to show differences in clinical outcomes or in responses to the ACTH test. Interestingly, the proportion of responders with low cortisol levels was higher than that in non-responders. Additionally, the proportional increase in cortisol levels after the ACTH test was inversely correlated with baseline cortisol levels. This finding emphasizes the idea that over-stimulated adrenal glands often do not further increase

cortisol levels even after supraphysiologic stimulation.^(2,14) We recently addressed this issue in another study comparing the diagnosis of CIRCI using both a low dose and a high dose of cosyntropin. LD and HD tests behave similarly in septic shock patients with intermediate baseline cortisol levels (10–34 µg/dL); we believe that stimulation tests are important to define CIRCI in this population.⁽¹⁴⁾ Dissociation in delta cortisol, induced by different doses of cosyntropin in patients with high baseline cortisol (>34 µg/dl), may be explained by the concept that such patients already have high baseline cortisol levels because they are already exposed to strong endogenous pituitary stimulation. Thus, 1 µg may not constitute an additional stimulation of the HPA axis, but 250 µg of cosyntropin, which simulates supraphysiological doses of ACTH, may increase cortisol production. In others words, the absence of an ACTH test response is not necessarily indicative of CIRCI when the patient is already overstressed. This result emphasizes the importance and difficulty of determining diagnostic criteria for adrenal insufficiency.

We did not measure the CBG and free cortisol levels, and we may have underestimated the baseline free cortisol levels and their increases upon ACTH administration.^(8,20-23) However, we used albumin levels to estimate free cortisol because albumin binds cortisol, although to a lesser extent than CBG, and both albumin and CBG levels may decrease to the same extent in critical illness.^(15,20-23) In our study, the basal cortisol/albumin ratio gave the best discrimination, as indicated by AUC analysis, but this discrimination was still only moderate. Basal cortisol levels and basal cortisol/albumin ratios correlated well, and both values were increased in non-survivors. Nevertheless, the predictive value of ACTH-cortisol responses in our study was not improved by dividing cortisol values by albumin levels.

Our study also has some other limitations associated with its retrospective design and multiple statistical tests. First, the decision to perform the ACTH test was based on clinical grounds. We did not exclude patients with very low baseline cortisol values (<10 µg/ml) because we were not able to attribute these values to primary or secondary adrenal insufficiency in the absence of free cortisol measurements corrected for disease severity. Additionally, the follow-up data of our patients after hospital release were not obtained. Finally, secondary outcomes, such as organ dysfunction, were not recorded. The results of this retrospective study confirm the idea that CIRCI diagnosis based on a standard ACTH test is common.

CONCLUSIONS

In ICU patients with septic shock, an increased basal cortisol level is associated with mortality and disease severity. Cortisol responses upon ACTH stimulation were not related to outcome. Clinically, the estimation of free cortisol levels using the cortisol/albumin ratio cannot predict unfavorable outcome better than total cortisol or help to improve the accuracy of the ACTH test. Our retrospective data confirms that the diagnosis of CIRCI based on a standard ACTH test is common.

RESUMO

Objetivo: Avaliar se as respostas do cortisol ao teste com 250 µg de hormônio adrenocorticotrófico, por via intravenosa, estão relacionadas à gravidade da doença e, conseqüentemente, à mortalidade.

Métodos: Estudo retrospectivo realizado em unidade de terapia intensiva de um hospital universitário. Foram estudados 69 pacientes consecutivos com choque séptico no período de 1 ano, submetidos a um teste rápido com 250 µg de hormônio adrenocorticotrófico, porque apresentavam >6 horas de instabilidade hemodinâmica progressiva, exigindo repetidos desafios hídricos e terapia com vasopressor para manter a pressão sanguínea. O teste foi realizado injetando-se 250 µg de hormônio adrenocorticotrófico sintético e avaliando-se o cortisol imediatamente antes, e 30 e 60 minutos depois da injeção.

Resultados: O escore APACHE II médio foi 22±7. A taxa de mortalidade na unidade de terapia intensiva foi de 55% no 28º dia. A mediana do cortisol basal (19 [11 a 27] µg/dL *versus* 24 [18 a 34] µg/dL; p=0,047) e a mediana da razão cortisol basal/albumina (7,6 [4,6 a 12,3] *versus* 13,9 [8,8 a 18,5]; p=0,01) foram mais baixas nos sobreviventes do que nos não sobreviventes. Respondedores e não respondedores tiveram dados clínicos basais e desfecho semelhantes. As variáveis significativamente relacionadas ao desfecho, baseadas na área sob curva ROC (AUC), foram: 0,67 [0,535 - 0,781] para APACHE II; 0,662 [0,536 - 0,773] para cortisol basal (µg/dL); 0,642 [0,515 a 0,755] para pico do cortisol (µg/dL); e -0,75 [0,621 - 0,849] para cortisol basal/albumina.

Conclusões: O aumento no cortisol basal está associado à mortalidade e à gravidade da doença. As respostas do cortisol após a estimulação por hormônio adrenocorticotrófico não se relacionaram ao desfecho. A razão cortisol basal/albumina não prevê resultados desfavoráveis melhor que o cortisol total e nem auxilia na acurácia desse teste.

Descritores: Insuficiência adrenal; Doença crítica; Hormônio adrenocorticotrófico/administração & dosagem; Hidrocortisona; Choque séptico

REFERENCES

1. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. *Chest*. 2002;122(5):1784-96.
2. Moraes RB, Czepielewski MA, Friedman G, Borba EL. Diagnosis of adrenal failure in critically ill patients. *Arq Bras Endocrinol Metabol*. 2011;55(5):295-302.
3. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. *Intensive Care Med*. 2006;32(2):275-80.
4. Rothwell PM, Udwardia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. *Lancet*. 1991;337(8741):582-3.
5. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA*. 2000;283(8):1038-45.
6. Journey TH, Cockrell JL Jr, Lindberg JS, Lamiell JM, Wade CE. Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. *Chest*. 1987;92(2):292-5.
7. Moran JL, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P. Hypocortisolemia and adrenocortical responsiveness at onset of septic shock. *Intensive Care Med*. 1994;20(7):489-95.
8. Oppert M, Reinicke A, Gräf KJ, Barckow D, Frei U, Eckardt KU. Plasma cortisol levels before and during "low-dose" hydrocortisone therapy and their relationship to hemodynamic improvement in patients with septic shock. *Intensive Care Med*. 2000;26(12):1747-55.
9. Bollaert PE, Fioux F, Charpentier C, Lévy B. Baseline cortisol levels, cortisol response to corticotropin, and prognosis in late septic shock. *Shock*. 2003;19(1):13-5.
10. Manglik S, Flores E, Lubarsky L, Fernandez F, Chhibber VL, Tayek JA. Glucocorticoid insufficiency in patients who present to the hospital with severe sepsis: a prospective clinical trial. *Crit Care Med*. 2003;31(6):1668-75.
11. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med*. 2003;31(1):141-5.
12. Goodman S, Sprung CL, Ziegler D, Weiss YG. Cortisol changes among patients with septic shock and the relationship to ICU and hospital stay. *Intensive Care Med*. 2005;31(10):1362-9.
13. Rady MY, Johnson DJ, Patel B, Larson J, Helmers R. Cortisol levels and corticosteroid administration fail to predict mortality in critical illness: the confounding effects of organ dysfunction and sex. *Arch Surg*. 2005;140(7):661-8; discussion 669.
14. Moraes RB, Friedman G, Tonietto T, Saltz H, Czepielewski M. Comparison of low and high dose cosyntropin stimulation tests in the diagnosis of adrenal insufficiency in septic shock patients. *Horm Metab Res*. 2012;44(4):296-301.
15. de Jong MF, Beishuizen A, Spijkstra JJ, Groeneveld AB. Relative adrenal insufficiency as a predictor of disease severity, mortality, and beneficial effects of corticosteroid treatment in septic shock. *Crit Care Med*. 2007;35(8):1896-903.
16. Marik PE. Critical illness-related corticosteroid insufficiency. *Chest*. 2009;135(1):181-93.
17. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2006;174(12):1319-26.
18. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348(8):727-34.
19. Azevedo JR, Azevedo RP, Cossetti RJ, Lima ER, Souza GB. Insuficiência adrenal relativa no choque séptico: comparação da resposta ao tratamento com hidrocortisona em pacientes diagnosticados através de dosagem única do cortisol plasmático versus teste da corticotropina. *Rev Bras Ter Intensiva*. 2008;20(1):18-23.
20. le Roux CW, Chapman GA, Kong WM, Dhillon WS, Jones J, Alagband-Zadeh J. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab*. 2003;88(5):2045-8.
21. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med*. 2004;350(16):1629-38.
22. Bendel S, Karlsson S, Pettilä V, Loisa P, Varpula M, Ruokonen E, Finnsepsis Study Group. Free cortisol in sepsis and septic shock. *Anesth Analg*. 2008;106(6):1813-9.
23. Beishuizen A, Thijs LG, Vermes I. Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. *Intensive Care Med*. 2001;27(10):1584-91.
24. Siraux V, De Backer D, Yalavatti G, Mélot C, Gervy C, Mockel J, et al. Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. *Crit Care Med*. 2005;33(11):2479-86.
25. Briegel J, Schelling G, Haller M, Mraz W, Forst H, Peter K. A comparison of the adrenocortical response during septic shock and after complete recovery. *Intensive Care Med*. 1996;22(9):894-9.
26. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862-71. Erratum in *JAMA*. 2008;300(14):1652. Chaumet-Riffaut, Philippe [corrected to Chaumet-Riffaut, Philippe].
27. Polito A, Aboab J, Annane D. Adrenal insufficiency in sepsis. *Rev Bras Ter Intensiva*. 2006;18(1):86-94.
28. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-24.
29. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-55. Review.
30. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-29.
31. Silva E, Pedro Mde A, Sogayar AC, Mohovic T, Silva CL, Janiszewski M, Cal RG, de Sousa EF, Abe TP, de Andrade J, de Matos JD, Rezende E, Assunção M, Avezum A, Rocha PC, de Matos GF, Bento AM, Corrêa AD, Vieira PC, Knobel E; Brazilian Sepsis Epidemiological Study, Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care*. 2004;8(4):R251-60.
32. Sales Junior JA, David CM, Hatum R, Souza PC, Japiassú A, Pinheiro CT, et al. Sepsis Brasil: estudo epidemiológico da sepse em Unidades de terapia intensiva brasileiras. *Rev Bras Ter Intensiva*. 2007;18(1):9-17.
33. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. *Clin Endocrinol (Oxf)*. 2004;60(1):29-35.
34. Bruno JJ, Hernandez M, Ghosh S, Pravinkumar SE. Critical illness-related corticosteroid insufficiency in cancer patients. *Support Care Cancer*. 2012;20(6):1159-67.
35. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327. Erratum in: *Crit Care Med*. 2008;36(4):1394-6.
36. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Art W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-49.
37. Moraes RB, Czepielewski MA, Friedman G. Is the cortisol test necessary in high basal corticoid patients with septic shock? *Crit Care Med*. 2009;37(1):385-6; author reply 386-7.