CORTISOL RESPONSE TO LOW-DOSE (1 μg) ACTH STIMULATION FOR THE PREDICTION OF OUTCOME IN PATIENTS WITH SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

ODGOVOR KORTIZOLA NA NISKODOZNI (1 μg) ACTH STIMULACIONI TEST U PREDIKCIJI ISHODA KOD BOLESNIKA SA SINDROMOM SISTEMSKOG INFLAMATORNOG ODGOVORA

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Summary

Background: Systemic inflammatory response syndrome (SIRS) changes cortisol dynamics and indicates dissociation between the adrenal cortex and the hypothalamo-pituitary unit. The aim of this study was to assess the cortisol response after stimulation with ACTH1-24 in patients with SIRS at admission to the Respiratory Intensive Care Unit (RICU) and seven days later.

Methods: Fifty-four subjects were included in the study, and SIRS was defined according to the Consensus Conference criteria from 1992. Severity of the disease was determined using the APACHE II score, and organ dysfunction using the SOFA score. Low-dose (1 μg) ACTH test (LDT) was performed in all patients, and cortisol was determined along with basal ACTH. Data were analyzed using parametric and nonparametric tests and regression analysis. The results are presented as mean ± standard deviation, and P<0.05 was considered statistically significant.

Results: There were no differences in cortisol values between the two LDTs. Cortisol increment lower than 250 nmol/L during the LDT was found in 14/54 (25.9%) subjects at the onset of SIRS. Five out of 54 (9.6%) patients died within 7 days from the onset of SIRS. Female sex and lower cortisol levels were associated with a worse outcome.

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List of abbreviations: SIRS, systemic inflammatory response syndrome; ACTH, adrenocorticotropic; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ICU/RICU, intensive care unit / respiratory intensive care unit; LDT, low-dose test; ARDS, acute respiratory distress syndrome.
maximal cortisol response ($\Delta_{\text{max}}$) on LDT predicted the duration of hospitalization in RICU, while APACHE II and SOFA scores best predicted the duration of hospitalization, mortality outcome as well as overall survival outcome.

**Conclusions:** A difference was found in $\Delta_{\text{max}}$ at the diagnosis of SIRS and seven days later. $\Delta_{\text{max}}$, and primarily the clinical scores APACHE II and SOFA predicted the outcomes of hospitalization and overall survival.

**Keywords:** cortisol, systemic inflammatory response syndrome, ACTH test, APACHE II, SOFA

### Introduction

Systemic inflammatory response syndrome (SIRS) represents an inflammatory condition that spreads all over the body. SIRS is most frequently caused by infection or sepsis. In comparison to the general term infection, sepsis is a condition in which the patient fulfills the criteria for SIRS, and has a known or very certain infection. SIRS is a serious condition that is related to systemic inflammation, organ dysfunction, and complete cessation of functions. SIRS is considered a part of the »cytokine storm«, and is manifested by the dysregulation of different cytokines (1). The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) defined SIRS using the following criteria: body temperature below 36 °C or over 38 °C, heart rate over 90 per minute, tachypnea over 20 respirations per minute or carbon dioxide partial pressure below 4.3 kPa (32 mmHg), and leukocyte number lower than 4000 cells/mm³ ($4 \times 10^9$ cells/L) or over 12,000 cells/mm³ ($12 \times 10^9$ cells/L), or presence of over 10% of immature neutrophils (1). The same societies accepted that severity of the disease is best predicted using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (2) while the patient’s outcome, namely organ dysfunction/failure during Intensive Care Unit (ICU) monitoring, is predicted using the Sequential Organ Failure Assessment (SOFA) score (3).

Systemic inflammatory response leads to significant changes in the concentrations of different hormones. Among them, the most characteristic is the cortisol change dynamics indicating dissociation between the adrenal cortex and the hypothalamo-pituitary unit. This is manifested by very high concentrations of cortisol and ACTH immediately after the initiation of SIRS. A few days later, however, ACTH falls to a very low concentration while the concentration of cortisol remains high (4). This is explained by the direct effect of cytokines on the adrenal cortex stimulating glucocorticoid release (5).

Cortisol response to stimulation with ACTH was shown to be an important predictor in critically ill patients (6). Patients with an inadequate cortisol response to stimulation with ACTH had a high mortality rate. The use of ACTH test, however, has not been standardized till now and has not been performed over different periods beginning with the onset of an inflammatory condition. Stimulation with 250 μg of ACTH is considered to be a standard test for the assessment of adrenal function (7, 8). The low-dose (1 μg) test (LDT), however, represents a more sensitive method for detecting specific forms of adrenal insufficiency such as hypothalamo-pituitary dysfunction (9, 10). The use of LDT in critically ill patients is not clearly defined as the data on LDT are limited and insufficient for a clear recommendation (11–13).

It is known that the response of cortisol to ACTH stimulation depends on the period that has elapsed since the occurrence of inflammation (6). The aim of this study was to assess the response of the adrenal cortex after stimulation with synthetic ACTH in patients with SIRS at admission to the Intensive Care Unit (ICU) and seven days later, and to follow the outcome of ICU hospitalization.

### Materials and Methods

**Study population**

Fifty-four consecutive patients (37 males, 17 females) were included in the study. All the investigated subjects were referred to the University Medical Center (UMC) »Bežanijska kosa«, Belgrade, due to the presence of fever, dyspnea and poor general condition. All of the patients were of Caucasian origin, with no history of malignant disease and previous therapy with ketoconazole, etomidate, and glucocorticoids. After the initial examination, most of the patients were admitted to the Respiratory Intensive Care Unit (RICU) of the UMC. If the patient was initially admitted to the Department of Pulmonology, but his clinical state soon deteriorated, he or she was transferred to the RICU. At admission to the RICU, vital status was assessed in all the patients, including state of consciousness, systemic arterial blood pressure and heart rate, and body temperature. In all the patients, community acquired pneumonia was confirmed.

SIRS was defined according to the 1992 ACCP/SCCM Consensus Conference (1) when the condition met two or more of the given criteria...
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ently.
of disease severity and mortality during stay in
APACHE II score (age, history of severe organ insuffi-
certainty, mean arterial pressure, heart rate, respiratory
rate, oxygenation, arterial pH, serum sodium, potas-
sium and creatinine, hematocrit, white blood cell
count and Glasgow Coma Scale score); (3) mortality
determination based on the degree of dysfunction of six
organ systems using the SOFA score (oxygenation,
platelets count, Glasgow Coma Scale score, bilirubin,
mean arterial pressure and creatinine); (4) need for
and length of mechanical ventilation, number of days
spent in the RICU, and the outcome of SIRS (survived
or non-survived).

The APACHE II score is expressed in points from
0 to 71, and a higher score implies more severe dis-
ease and higher mortality risk. The SOFA score is
used in monitoring patient status during the stay in
the ICU. Both APACHE II and SOFA provide an esti-
mate of disease severity and mortality during stay in
the ICU based on a number of the abovementioned
laboratory values and patient signs, taking both acute
and chronic disease into account.

Laboratory variables. At admission to the hospi-
tal and the diagnosis of SIRS, hematologic and chem-
istry data, and blood gas determinations were done
systematically. Low-dose ACTH test was performed in
all patients immediately after the admission to the
RICU and seven days later.

ACTH testing procedure. At admission to the
RICU, an indwelling venous catheter was placed in
the antecubital vein and, in all the patients, blood
samples were drawn for the determination of stan-
dard biochemical analyses, cortisol and ACTH. At
least 30 min after placing the catheter, the LDT was
started with an IV injection of 1 µg ACTH1-24
(Synacthen, Novartis Pharma Schweiz AG). Blood
samples for cortisol determination were taken from
the IV cannula at 0, 15 and 30 min. All blood sam-
plies were immediately separated and kept frozen at
–80 °C until assayed. As previously described, for the
low-dose ACTH test, a vial of 250 µg Synacthen was
diluted in normal saline solution to a concentration of
0.5 µg/mL (10), and the solution was used immedi-
ately.

Study protocol was approved by the Ethical
Committee of the Faculty of Medicine, University of
Belgrade, and informed consent was obtained from
each patient or patient’s next-of-kin.

Assays

Cortisol was determined using an immunoassay
(Elecsys Cortisol II assay, Cobas e411 analyzer, Roche
Diagnostics GmbH, Mannheim, Germany), with intra-
and inter-assay CV of 1.8–7.1% and 2.7–12.7%,
respectively. ACTH was also determined using an
imunoassay (Elecsys ACTH assay, Cobas e411 ana-
lyzer, Roche Diagnostics GmbH, Mannheim, Germany)
with intra- and inter-assay CV of 2.0–2.9% and
2.4–5.4%, respectively.

Statistical analysis

Statistical analysis was performed using R (14),
Vienna, Austria (https://www.R-project.org/). For
comparison between groups, Student t test was used
for two independent samples for parametric data, and
χ² test was employed for nonparametric data and
binomial variables. Results are presented as mean ±
standard deviation (x ± SD) for the continuous vari-
able, and as percentages for the binary variables.

Zero-inflated negative binomial regression was
used for modeling count variables with excessive
zeros, and for overdispersed count outcome variables.
We investigated the possibility of predicting whether a
patient will receive mechanical ventilation during
his/her stay in the RICU and for how many days,
based on patient characteristics collected at the onset
of SIRS presented with APACHE II and SOFA scores.

Poisson regression model was used for prediction
of days spent in the RICU based on sex and maximal
cortisol increase during the ACTH stimulation test.

Logistic regression analysis was performed to
predict overall outcome (survival or death). Cali-
 bration of the logistic model was assessed using the
Hosmer-Lemeshow goodness-of-fit test to evaluate
the importance of the discrepancy between observed
and expected mortality.

For all tests, P<0.05 was considered statistically
significant.

Results

The clinical and biochemical characteristics of
SIRS patients are presented in Table I. Respiratory
infections were confirmed in all patients. Of 54
patients, 5 (9.6%) died within the 7-day period follow-
ing the onset and management of SIRS in the RICU.

In respect to hormonal analysis, we evaluated
both the basal values of ACTH and cortisol, and cor-
tisol values at each time point of the ACTH test. Basal
ACTH concentrations did not differ between admis-
### Table I Clinical and biochemical characteristics of the whole group of patients at baseline and after 7 days in RICU.

| Variable                        | N  | 45.25±5.45 | 54 |
|---------------------------------|----|------------|----|
| Age (years)                     |    |            |    |
| Sex                             |    |            |    |
| Male, N (%)                     | 37 (67.3) |           |    |
| Female, N (%)                   | 17 (32.7) |           |    |
| Onset of disease (days)         | 4.25±1.31 |           |    |
| Underlying disease              |    |            |    |
| Community acquired pneumonia, N (%) | 48 (92.3) |           |    |
| ARDS, N (%)                     | 3 (5.8) |           |    |
| Sepsis, N (%)                   | 1 (1.9) |           |    |
| APACHE II                       |    |            |    |
| Point                           | 15.79±6.16 |           |    |
| %                               | 25.19±17.5 |           |    |
| SOFA                            |    |            |    |
| Point                           | 3.48±2.04 |           |    |
| %                               | 11.92±7.93 |           |    |
| Mechanical ventilation          |    |            |    |
| Yes / No                        | 9 (16.7) | 45 (83.3) |    |
| Duration (patients on ventilation) (days) | 5.14±4.49 |           |    |
| Duration (whole group) (days)   | 0.69±2.35 |           |    |
| Outcome                         |    |            |    |
| Survived, N (%)                 | 49 (90.4) |           |    |
| Died, N (%)                     | 5 (9.6) |           |    |
| ACTH (ng/dL)                     | 6.57±7.08 | 6.46±8.72 |    |
| Synacthen test                   |    |            |    |
| Cortisol (nmol/L), 0 min        | 633.22±362.30 | 582.62±341.56 |    |
| Cortisol (nmol/L), 15 min       | 832.25±311.89 | 805.35±328.51 |    |
| Cortisol (nmol/L), 30 min       | 896.57±305.36 | 854.54±313.16 |    |
| Cortisol (nmol/L), 60 min       | 884.69±339.29 | 841.11±363.53 |    |
| Maximal cortisol (mean)         | 967.75±321.02 | 932.65±348.12 |    |
| Difference cortisol (maximal value – basal value) | 353.47±193.7 | 350.04±262.96 |    |
| Difference cortisol (maximal value – 15 min value) | 220.92±133.36 | 222.73±152.52 |    |
| Difference cortisol (maximal value – 30 min value) | 285.25±147.13 | 271.93±175.85 |    |
| Difference cortisol (maximal value – 60 min value) | 270.41±222.04 | 258.49±289.77 |    |
| Maximal cortisol (Δ max) (Day 0 – Day 7) | 582.62±341.56 |           |    |

RICU, respiratory intensive care unit; ARDS, acute respiratory distress syndrome; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ACTH, adrenocorticotropicin.
Table II Inflated Negative Binomial Regression analysis for the prediction of mortality using APACHE II score.

| Variable                     | Regression Coefficient (β) | SE   | Odds Ratio (95% Confidence Interval) | P Value |
|------------------------------|-----------------------------|------|-------------------------------------|---------|
| Count Model Coefficients     |                             |      |                                     |         |
| Intercept                    | -0.085                      | 0.658| -0.130                              | 0.896   |
| Sex (female)                 | -0.734                      | 0.504| -1.467                              | 0.145   |
| Maximal cortisol difference  | 0.005                       | 0.001| 3.286                               | 0.001   |
| Zero-Inflation Model Coefficients |                      |      |                                     |         |
| Intercept                    | 19.696                      | 9.285| 2.121                               | 0.033   |
| APACHE II                    | -0.931                      | 0.470| -1.981                              | 0.047   |

APACHE, acute physiology and chronic health evaluation.

Table III Inflated Negative Binomial Regression analysis for the prediction of mortality using SOFA score.

| Variable     | Regression Coefficient (β) | SE   | Odds Ratio (95% Confidence Interval) | P Value |
|--------------|----------------------------|------|-------------------------------------|---------|
| Count Model Coefficients |                      |      |                                     |         |
| Intercept    | -0.969                     | 1.010| -0.960                              | 0.337   |
| Sex (female) | -4.122                     | 1.352| -3.048                              | 0.002   |
| Maximal cortisol difference | 0.004                 | 0.001| 3.348                               | <0.001  |
| Zero-Inflation Model Coefficients |                      |      |                                     |         |
| Intercept    | 7.097                      | 3.090| 2.296                               | 0.021   |
| SOFA         | -1.335                     | 0.732| -1.824                              | 0.068   |

SOFA, sequential organ failure assessment.

Table IV Poisson regression analyses for the prediction of the duration of stay in RICU.

| Variable             | Regression Coefficient (β) | SE   | Odds Ratio (95% Confidence Interval) | P Value |
|----------------------|----------------------------|------|-------------------------------------|---------|
| Intercept            | 0.986                      | 0.174| 5.653                               | <0.001  |
| Sex (female)         | -0.106                     | 0.190| -0.559                              | 0.576   |
| Maximal cortisol difference | 0.0004                | 0.0002| 1.967                               | 0.049   |
| Inclusion of APACHE II score |                      |      |                                     |         |
| Intercept            | 0.400                      | 0.233| 1.715                               | 0.086   |
| Sex (female)         | -0.087                     | 0.192| -0.453                              | 0.650   |
| Maximal cortisol difference | 0.0001               | 0.0002| 0.391                               | 0.696   |
| APACHE II            | 0.048                      | 0.013| 3.594                               | <0.001  |
| Inclusion of SOFA score |                      |      |                                     |         |
| Intercept            | 0.643                      | 0.207| 3.101                               | 0.001   |
| Sex (female)         | -0.065                     | 0.191| -0.343                              | 0.731   |
| Maximal cortisol difference | 0.0002               | 0.0002| 1.237                               | 0.216   |
| SOFA                 | 0.113                      | 0.035| 3.149                               | 0.001   |

RICU, respiratory intensive care unit; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.
sion time to the RICU and at follow-up seven days later. Basal cortisol concentrations and cortisol values during the LDT did not differ at the two time points during follow-up. The cortisol increment defined as a difference between maximal value and the values at each sampling time point did not differ between the two tests 7 days apart. In the whole group of patients, cortisol increment lower than 250 nmol/L during the ACTH test was found in 14 (25.9%) subjects on Day 0, and in 13 (24%) subjects on Day 7. In patients who died during the follow-up period, cortisol increment lower than 250 nmol/L was recorded in 3/5 subjects (60%).

APACHE II and SOFA scores were significantly associated with prediction of mortality during hospitalization in the RICU, and are related to the maximal cortisol increase during ACTH testing (Table II and Table III). Female sex and maximal cortisol response on ACTH testing predicted duration of hospitalization in the RICU, namely, the higher the maximal cortisol response, the longer the period of hospitalization in the RICU (Table IV). In the logistic regression, APACHE II and SOFA scores were the only significant variables associated with prediction of the overall survival outcome (Table V).

**Discussion**

Our study was designed to assess the response of cortisol after low-dose ACTH stimulation in patients admitted to the RICU because of a fully clinically defined state of SIRS due to a respiratory infection. Although we did not find differences in either basal cortisol values or at each time point of the ACTH test, a difference in the maximal cortisol response (Δ max) during the ACTH test before and after 7 days of follow-up was clearly shown. Moreover, Δ max predicted the duration of hospitalization in the RICU and in-hospital mortality outcome. The clinical scores APACHE II and SOFA, however, were shown to be the best predictors of duration of hospitalization, mortality outcome as well as overall survival outcome.

SIRS implies a clinical response to a nonspecific insult characterized with two or more of the defined variables, while sepsis represents SIRS with a documented infection. Consequently, multiple organ dysfunction syndrome (MODS) represents a sequel of SIRS and/or sepsis, and failure to maintain homeostasis without intervention. Hence, MODS is recognized as a sequel to SIRS, a continuum that includes the development of SIRS, onset of sepsis and progression to septic shock, and multiple organ dysfunction (15), and it is related to high mortality (16). However, data on the prevalence of SIRS and sepsis are still lacking. According to some European analyses, severe infection is diagnosed in 16% of patients hospitalized in the ICU due to respiratory complications as the most common feature, with deadly outcome in approximately half of them (17).

Our group of patients had SIRS caused by a respiratory infection, and all of them continue their monitoring and treatment in the RICU. The mortality rate calculated from the APACHE II score was higher than the mortality recorded in our study. A possible explanation could be the design of the study that followed patients for seven days in comparison to other studies that followed patients for 28 days after the onset of SIRS or sepsis. Moreover, estimated organ dysfunction predicted by the SOFA score and the mortality rate predicted by the APACHE II score suggest possibly milder forms of SIRS at presentation within our group of patients.

It was observed that increased levels of plasma cortisol are related to higher risk of death in critically ill humans. Inappropriately low cortisol concentrations, however, were shown to be related to increased mortality as well (18). A new clinical description of ‘critical illness-related corticosteroid insufficiency’ (CIRCI) was used to define higher cortisol levels in this condition in comparison to healthy status (19). Diagnostic criteria for CIRCI in the critically ill were based on a cortisol incremental response of less than 9 mg/dL (250 nmol/L) after adrenal cortex stimulation with 250 μg ACTH, and this was considered the
most discriminative for increased risk of death (20). During the ACTH test, a cortisol increment lower than 250 nmol/L was observed in 14/54 (25.9%) of our patients. Similar prevalence of relative adrenal insufficiency or dysfunction (less than 25%) was observed in ICU patients with diagnosis other than septic shock (13). In our group of patients, however, death as outcome was recorded in 3/5 (60%) of those with a cortisol increment lower than 250 nmol/L. Relatively lower values for deadly outcome in our patients could be related to the SIRS condition, in comparison to other studies that recorded deadly outcomes in 100% of patients with sepsis (21). Moreover, the Δ maximal cortisol increment obtained in our study far exceeds the cutoff point increment proposed for the assessment of outcome of the critically ill (20, 21) and is in line with the low prevalence of relative adrenal insufficiency in our patients with SIRS. The Δ maximal cortisol increment could be used for the prediction of length of hospitalization in the RICU and mortality outcome. However, when included into the respective analyses, the scores APACHE II and SOFA best predicted the duration of hospitalization in the RICU, mortality outcome and overall survival outcome, and the same has been shown elsewhere (2–5, 23).

Taking into consideration the above facts about the adrenal axis changes during SIRS, a high sensitivity test should be performed for the diagnosis of adrenal cortex dysfunction. It was shown that LDT with 1 μg of ACTH is more sensitive for detecting mild secondary adrenal insufficiency, and is superior to the standard stimulation test with 250 μg of ACTH (10). The patients we investigated represented a natural model of secondary adrenal insufficiency. As expected, we showed low normal levels of ACTH at both time points (Day 0 and Day 7). Although cortisol concentrations during the ACTH test showed a trend towards decrease after seven days, they did not reach statistical significance. In the repeated test, however, only the maximal cortisol response during the ACTH test showed a clear decrease. Our results are in line with a recent study on ACTH and cortisol concentrations during the first seven days of ICU monitoring. Namely, morning ACTH was suppressed from admission to the intensive care unit and remained below the limit of normality during the first week of critical illness (24). Although our results showed a similar pattern of low ACTH from the beginning of the follow-up period, it could be assumed that we had missed the initial ACTH response to stress prior to admission to the ICU, and the same was supposed by others as well (24). This possibility was recently supported by the detection of low orexin activity in the hypothalamus during a prolonged phase of critical illness that happened 48 hours after the initial rise in ACTH (25).

Besides ACTH, the cortisol production rate in ICU patients was moderately increased but without the doubling of values that was observed in healthy subjects (24). Moreover, cortisol production was elevated only in patients with SIRS, possibly mediated by the activity of cytokines (1, 24). Accordingly, low ACTH and high cortisol suggest that mechanisms other than those dependent on ACTH are responsible for the high cortisol concentrations during critical illness, namely, growth factors, corticotrophin releasing hormone and ACTH loop, immune system or the local vascular system characteristics (26, 27). Nevertheless, other possibilities such as suppressed cortisol clearance with consequently elevated plasma cortisol concentrations and suppressed ACTH release should also be considered (24).

**Conclusion**

We showed a difference in the maximal cortisol response (Δ max) between two LDTs performed at the diagnosis of SIRS and seven days later. The Δ max, and primarily the clinical scores APACHE II and SOFA predicted clinical outcomes of hospitalization in the RICU, while the clinical scores also successfully predicted overall survival outcome. LDT represents a sensitive tool for detecting specific forms of adrenal insufficiency as it could be induced by the state of SIRS.

**Acknowledgements.** This work was supported by the Serbian Ministry of Science and Education (Grants 41009 and 175032).

**Conflict of interest statement**

The authors stated that there are no conflicts of interest regarding the publication of this article.

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