Cortisol-Mediated Stress Response and Mortality in Acute Coronary Syndrome

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Abstract: Acute coronary syndrome is a frequent cause of morbidity and mortality, and a known stress response trigger. We aim to investigate the association between cortisol, as a primary stress hormone, and prognosis/mortality in this scenario. Single-center, prospective, observational, and analytical study in patients admitted for acute coronary syndrome. Clinical characteristics and prognosis markers were registered, along with serum cortisol levels on admission and in-hospital mortality. Cortisol levels were higher in patients with a depressed ST segment (18.22 ± 13.38 μg/dL), compared to those with an isoelectric ST segment (12.66 ± 10.47 μg/dL), and highest in patients with an elevated ST segment (22.61 ± 14.45 μg/dL), with $P <$ 0.001. Also, cortisol was significantly increased in patients with elevated troponin I values (18.90 ± 14.19 μg/dL vs 11.87 ± 8.21 μg/dL, $P <$ 0.001). Patients with Killip-Kimball class I or II had a lower mean serum cortisol (14.66 ± 10.82 μg/dL) than those with class III or IV (41.34 ± 15.57 μg/dL), $P <$ 0.001. Finally, we found that patients who died during

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hospitalization had higher cortisol on admission: 36.39 ± 17.85 μg/dL vs 15.26 ± 11.59 μg/dL, *P*= 0.003. Cortisol was directly related to the electrocardiographic presentation of ACS and with the maximum troponin I value. This indicates that serum cortisol levels parallel the extension of ischemia and myocardial injury, and in this way affect the clinical prognosis, evidenced by the Killip-Kimball class and the increase in mortality. (Curr Probl Cardiol 2021;46:100623.)

Background

Cardiovascular disease and acute coronary syndrome (ACS) are among the leading global causes of morbidity and mortality. They are a hazard for the health and survival of the population and therefore originate a genuinely stressful situation. Cortisol is a steroid hormone of the glucocorticoid class and is considered the primary stress hormone.[1,2] As such, it plays an important role in the stress response triggered by an ACS, although there is a paucity of recent information about its effects in this scenario.[3] It was suggested that it could have an influence on the size of the infarcted myocardium and be related to prognosis.[4-6] The objective of our investigation is to study the behavior of serum cortisol in patients with an ACS in the current era and to determine its relation to clinical characteristics, prognostic markers, and mortality.

Methods

We conducted a single-center, prospective, observational, and analytical study in a University Hospital in Buenos Aires, Argentina. All patients admitted to the coronary care unit (CCU) with a diagnosis of ACS were included. The exclusion criteria were current use of steroids, presence of underlying inflammatory disease, infection or cancer, or the patient's decline of consent to participate.

The subject's demographic data and clinical variables were collected from the medical records, such as age, sex, electrocardiographic parameters, and troponin I values. Positive troponin I was defined as being above the 99th percentile for the reference laboratory test. On arrival to the CCU and irrespective of the time of day, blood samples were obtained to measure total serum cortisol levels in all patients (chemiluminescence method) and high-sensitivity C-reactive protein (turbidimetry) was measured in a randomly selected subgroup. A second sample was obtained at

8 AM after 48 hours from admission for cortisol determination. The Killip-Kimball class of each patient was assessed on admission and every day afterward by the attending physicians, and the maximum class during hospitalization was considered for the analysis. Every death during hospitalization was registered. One-year follow-up was performed via phone calls and review of the hospital medical records.

The principles of the Declaration of Helsinki (Fortaleza, 2013) and local regulations were observed throughout the study. The Ethics Committee of the Hospital approved the study protocol. All patients gave their written informed consent to participate.

For statistical analysis, continuous normal variables were summarized as means and standard deviations (±SD), and categorical variables as absolute and relative frequencies (%). Comparisons of continuous variables were performed with Student's *t* test or the Wilcoxon rank-sum test, according to their distribution. Multiple comparisons were performed with ANOVA. Correlation was assessed with Pearson's coefficient (PCC). Statistical significance was considered with a P value of < 0.05. All calculations were done with R version 3.5.1.

Results

A total of 236 patients were included. The general characteristics of the population are outlined in Table. The mean age was 69.2 ± 12.5 years, 57.9% were male, 66.2% had hypertension, 25.2% dyslipidemia, 27.4% diabetes, and 20.1% were smokers. Most patients received DAPT (98% with aspirin and 82.8% with P2Y12 inhibitors) and the majority who had one or more vessels with >70% stenosis underwent revascularization (70.5%). Total mortality during hospitalization was 5.1%, and cardiovascular mortality was 4.5%.

Cortisol levels were higher in patients with a depressed ST segment (18.22 ± 13.38 μg/dL), compared to those with an isoelectric ST segment on arrival (12.66 ± 10.47 μg/dL), and highest in patients with an elevated ST segment (22.61 ± 14.45 μg/dL), with $P < 0.001$ (Fig 1A).

Also, cortisol was significantly increased in patients with positive troponin I values (18.90 ± 14.19 μg/dL vs 11.87 ± 8.21 μg/dL, $P < 0.001$), as can be seen in Figure 1B. Additionally, troponin and cortisol levels showed a significant correlation (PCC of 0.33, $P < 0.001$), as observed in Figure 2.

Figure 1C shows the association between maximum Killip-Kimball class and cortisol levels. Patients with Killip-Kimball class I or II had a

TABLE. Population characteristics

Characteristic (n = 236)	mean (±SD) or n (%)
Age (y)	69.2 (±12.5)
Male	136 (57.9%)
Hypertension	155 (66.2%)
Dyslipidemia	59 (25.2%)
Smoker	47 (20.1%)
Former smoker	88 (37.6%)
Diabetes	64 (27.4%)
Renal failure	17 (7.3%)
COPD	13 (5.6%)
Stroke	21 (9.0%)
Heart failure	12 (5.1%)
Stable coronary disease	41 (17.5%)
STEMI	63 (27.0%)
Killip-Kimball class	
I	185 (80.4%)
II	29 (12.6%)
III	6 (2.6%)
IV	10 (4.3%)
Elevated troponin	149 (65.9%)
Cinecoronarography performed	171 (73.1%)
Hospital mortality	12 (5.1%)
Cardiovascular mortality	11 (4.5%)

lower mean serum cortisol (14.66 ± 10.82 μg/dL) than those with class III or IV (41.34 ± 15.57 μg/dL), with $P < 0.001$.

We found that patients who died during hospitalization had higher cortisol on admission: 36.39 ± 17.85 μg/dL vs 15.26 ± 11.59 μg/dL, $P = 0.003$ (Fig 1D). Of note, hospital mortality with cortisol levels above its cut-off value of 20 μg/dL (n = 55) was 14.8%, while with lower levels it was 2.0% ($P = 0.001$).

One-year follow-up was complete for 81% patients, and similar results were obtained when analyzing admission cortisol levels by one-year mortality: 26.76 ± 15.94 μg/dL vs 15.24 ± 12.19 μg/dL, $P = 0.002$.

There was no significant correlation between cortisol and age (PCC = 0.13, $P = 0.06$), and the cortisol levels were similar in both sexes ($P = 0.96$). Cortisol on admission did not significantly differ from morning cortisol after 48 hours (16.43 ± 12.85 μg/dL vs 15.01 ± 9.80 μg/dL, $P = 0.46$).

Hs-CRP was measured in a subgroup of 106 patients. Its levels were higher in patients who died during hospitalization (21.33 [interquartile range 3.86-83.94] vs 4.77 [interquartile range 1.64-16.65]), although the difference was not statistically significant ($P = 0.24$). There was a positive

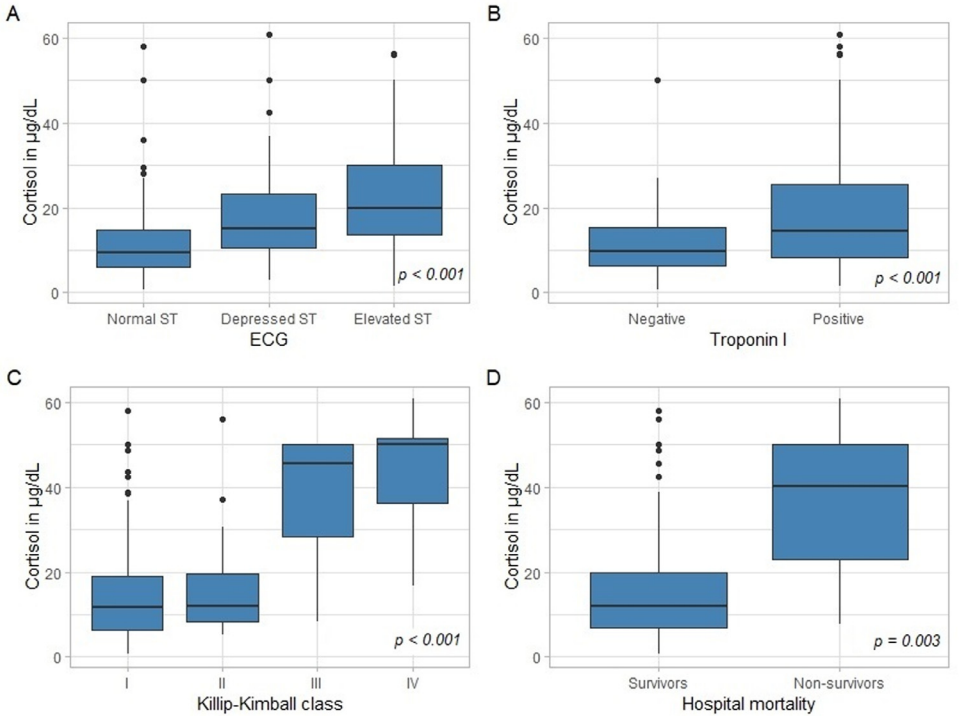

FIG 1. Cortisol levels according to (A) electrocardiogram, (B) troponin I, (C) Killip-Kimball class, and (D) mortality.

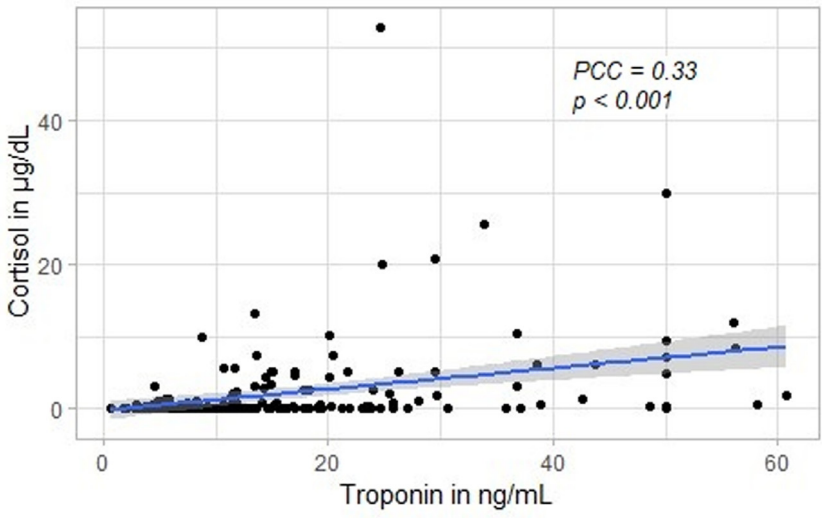

FIG 2. Correlation between troponin and cortisol levels.

and significant correlation between cortisol and hs-CRP levels (PCC = 0.32, $P < 0.001$).

Discussion

Since the initial description by W. Cannon of the "fight or flight syndrome" and later H. Selye's "general adaptation syndrome," the stress response has become one of the most interesting chapters of human physiology. This complex and stereotyped response, shared by many living organisms, has allowed our ancestors to survive multiple situations such as food shortages, infections, and predator attacks.[7,8] Thousands of years later, this same response in is triggered against a vital threat of more recent appearance in our evolutionary history such as the ACS. Thus arises our interest to study its effects in this clinical situation, one of the major current threats to our survival.

In ACS, the electrocardiogram can identify ischemic changes that are evidenced by abnormalities in the ST segment. It is clear that the ST segment deviation reflects the severity of the ischemia and the patient's prognosis.[9,10] It is interesting to note that cortisol, as a stress response marker in ACS, discriminates the same populations as the electrocardiogram does (isoelectric, depressed or elevated ST).

When assessing the behavior of cortisol against cardiac biomarkers, we found that it can differentiate patients based on the troponin I positivity, and that cortisol is correlated to the maximum troponin I values, indicating the amount of compromised myocardium. These results confirm previous findings by Stubbs and col. who studied the relationship between cortisol and maximum creatine phosphokinase (CPK) values 2 decades ago.[11] This could be explained, at least partially, by the relation between serum troponin and myocardial injury, independently from the presence of ischemia that motivated admission to the CCU. The tissue damage leads to the release of damage-associated molecular patterns,[12] which give rise to a systemic inflammatory response that activates the hypothalamic-pituitary-adrenal axis, promoting the stress response.[13-16] This could justify the correlation we observed between cortisol as a stress response marker and CRP as an inflammation marker, since IL-6 is the principal stimulus for its secretion.[17] Furthermore, though we cannot quantify the amount in which psychological stress is involved in this situation, in previous studies, it was demonstrated that cortisol levels can differentiate patients with an ACS from those with chest pain of other causes with no CPK elevation or electrocardiographic changes.[11,18]

In healthy individuals, cortisol secretion follows a circadian rhythm, with maximal levels early in the morning and lowest during sleep. In critical illness, the circadian rhythm of cortisol secretion is lost, and in the ACS its levels persist high for several days, as we observed, with no differences between cortisol at the time of admission and morning cortisol after 48 hours.[15,19]

In the acute phase of critical illness plasma cortisol concentrations are proportional to illness severity.[15,20,21] In our study, admission cortisol levels were also associated with the maximum Killip-Kimball class during hospitalization. Since the Killip-Kimball class is a well-known severity and prognostic marker, it would be reasonable to expect to find this association to closely correspond to the one between cortisol levels and the presence of ischemia and myocardial injury, assessed by ST-segment changes and troponin I values.[10,22]

There is a paucity of recent evidence regarding the association between cortisol and mortality in ACS.[5,6,23] We observed that, as in other diseases, cortisol can predict both in-hospital and 1-year mortality.[21,24] We believe that these findings justify further study of this stress response marker, and also allow a different approach to risk prediction that does not focus only on specific manifestations of ACS, but also on its biological impact, as well as the intensity of the mounted stress response which appears to be proportional to the threat.

In this fashion, our results reaffirm previous findings and contribute new insights to the association between cortisol and clinical outcomes in ACS, as a primary effector of the stress response. Nevertheless, new questions are posed. Is cortisol only a stress marker in ACS, or does it also have specific effects on the ischemic myocardium? On this subject, Weir and cols. have demonstrated that not only aldosterone but also cortisol may have a role in ventricular remodeling after infarction, and that this effect of both hormones could be prevented with the use of mineralocorticoid antagonists such as eplerenone, already proven to reduce mortality after ACS.[25,26]

Our study has some limitations. The characteristics of the population do not permit its findings to be generalized to other practices. Also, the sample size and the variable distributions did not allow modeling to evaluate the independent effects of cortisol over mortality.

Conclusion

Cortisol was directly related to the electrocardiographic presentation of ACS, with maximum values in STEMI, intermediate with a depressed ST and lowest with an isoelectric ST. Furthermore, we found cortisol was correlated with the maximum troponin I value, confirming its previously described increase with higher CPK values. This indicates that serum cortisol levels parallel the extension of ischemia and myocardial injury, and in this way affect the clinical prognosis, evidenced by an increase in mortality.

Cortisol is an excellent stress response marker in ACS, with a relevant role in its diagnosis and prognosis. Nonetheless, there is a lack of knowledge about its particular effects in the myocardium as well as regarding its possible role in the therapy for ACS.

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