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Adrenal Insufficiency in Cardiogenic Shock: Incidence and Prognostic Implication

Emad Omer, Hanan Zaghla

Critical Care Medicine Department, Faculty of Medicine, Cairo University, Giza, Egypt
Email: hananzaghla@hotmail.com

Abstract

Introduction: Functional integrity of the hypothalamic pituitary axis is disrupted during severe infection or stress. The observed blunted response to corticotropin was interpreted as impaired secretory reserve of the adrenal glands and was termed as relative adrenocortical insufficiency. **Aim of the work:** To study the incidence of adrenal insufficiency in patients developed cardiogenic shock complicating ST segment elevation myocardial infarction. **Materials and methods:** Prospective cohort study was done for 90 patients admitted to Algalaa Hospital for whom basal cortisol and ACTH level were measured immediately before a standard-dose (250 μg) ACTH stimulation test (SST) and 60 minutes after SST Δmax is defined as the difference between the maximal value after the test and basal level of serum cortisol. **Results:** Baseline ACTH and total cortisol showed positive correlation to clinical severity scores (APACHE II and Lactate), LVEF as well as vasoactive inotrope score, all with significant p value (0.000). The higher baseline cortisol level was co-related to increased mortality (Baseline serum cortisol level was significantly lower in survivors (30.6 ± 6.1 vs 45.0 ± 16.3) p value: 0.000) while the better response of the adrenal gland to short stimulation test was co-related more to survival as detected by Δmax TC (difference of cortisol level before and after SST) (13.8 ± 3.8 in survivors vs 8.5 ± 4.42 in non survivors) p value 0.000. **Conclusion:** A high baseline plasma TC was associated with increased mortality in patients with cardiogenic shock post acute myocardial infarction. Patients with lower baseline TC, but with a better adrenal response, appeared to have a survival benefit.

Keywords

Adrenal Insufficiency, Cardiogenic Shock, Myocardial Infarction, Short Stimulation Test, Cortisol, ACTH

1. Introduction

The concept of Relative Adrenal Insufficiency (RAI) in critical illness is still a matter of debate. In a common study published by Boonen *et al.*, it was demonstrated that cortisol clearance is declined to 40% in critically ill patients with hyperlactatemia and 34 points APACHE II score. The decreased clearance was deemed responsible for the elevated cortisol levels frequently found in critical illness and the lower cortisol clearance was also associated with less cortisol response to corticotropin [1]. Although high cortisol levels appear to argue against a syndrome of corticosteroid insufficiency, the combination of high serum cortisol levels and a blunted response to corticotropin showed the worst prognosis in septic shock [2]. Despite these new insights into cortisol metabolism during critical illness, the prognostic value of a short corticotropin test has been demonstrated in many studies in septic shock, it should be further studied in other types of shock like cardiogenic shock.

AIM of the work: was to study the incidence of relative adrenal insufficiency in patients with cardiogenic shock following acute myocardial infarction and its effect on the prognosis.

2. Materials and Methods

This was a prospective observational cohort study where 90 patients (age more than 18 years) were admitted to Algalaa and Kasralainy hospitals from January 2018 to January 2019 fulfilled the diagnostic criteria of cardiogenic shock (secondary to ST-elevation myocardial infarction (STEMI)) criteria for cardiogenic shock are sustained hypotension (systolic blood pressure < 90 mm Hg for ≥30 min) and a reduced cardiac index (<2.2 L/min/m^2) in the presence of normal or elevated pulmonary capillary wedge pressure (>15 mm Hg) or right ventricular end-diastolic pressure (RVEDP) (>10 mm Hg) [3].

Exclusion Criteria: patient with non ST segment elevation MI, Patients were on herbal medication or steroid treatment up to six months prior to the admission; patients with: history of hypothalamus-pituitary, adrenal dysfunction, liver diseases (ALT ≥ twice normal upper limit), systemic inflammatory response syndrome (SIRS; temperature ≥ 38˚C or ≤36˚C, heart rate > 90 beats/min, respiratory rate ≥ 20 breaths/min, PaCO2 ≤ 32 mm Hg, white blood cell count ≥ 12,000/μL or ≤4000/μL or >10% immature forms) basal cortisol and ACTH level were measured for all included patients immediately before a standard-dose (250 μg) ACTH stimulation test (SST) and 60 minutes after SST Δmax is defined as the difference between the maximal value after the test and basal level of serum cortisol [3].

All patients were also subjected for:

Serial ECG and cardiac enzyme and echocardiography Routine laboratory investigations including CBC, coagulation profile, and lipid profile Kidney function tests, liver function tests, arterial blood gases and serum lactate Routine calculation of the APACHYII score was calculated in the first 24 hours [4], **Figure 1**.

Figure 1. Parameters of APACHE II score.

Vasopressor score: calculated by the sum of the doses of adrenaline, noradrenaline, dopamine, dobutamine, milrinone, and vasopressin of the patients within the ICU stay. Overall VIS values were obtained by using the mean value of each agent.

Statistical analysis:

All collected questionnaires were revised for completeness and accuracy. Pre-coded data were collected and verified prior to analysis, statistical analyses were performed using SPSS software for windows, version 15.0 (SPSS Inc., Chicago IL, USA).

P value less than 0.05 was considered of statistically significance. A multiple regression model was built to identify potential significant predictors of mortality (SPSS Inc., Chicago, IL, USA).

3. Results

Demographic data; the included patients were 60.1 ± 15.5 years old (56.9 - 63.4), the study comprised 52 males (57.8%).

1) Descriptive data:

The mean APACHE II for included patients was 80.8 ± 17.1, The mean LVEF was $32.2\% \pm 6.9\%$, The mean Fluid balance day 1685.2 ± 914.5 ml/day (+ve balance), the mean ACTH baseline ng/L 40.1 ± 20.4, The mean Total cortisol bl ug/dl was 37.8 ± 14.2, the mean TC 60 min post SST was 48.9 ± 12.9, the mean Δmax TC was 11.1 ± 4.9, the mean Steroid replacement was needed in 12 patients (13.3%), the mean Lactate was 7.3 ± 2.8, the mean Arterial PH was 7.3 ± 0.1, the mean PO2/Fio2 was 174.5 ± 57.8, MAP was 57.9 ± 5.3 mmhg, the mean HR was 102.1 ± 19.2 beat/minute, the mean BMI was 31.1 ± 4.7, the mean troponin was

50.0 ± 27.7 ng/ml, the mean serum creatinine was 5.0 ± 18.1, INTRA-aortic balloon counterpulsation30 (33.3%), cardiac arrest occurred for 45 patients (50.0%) and 42 patients died (Mortality 46.7%) Table 1.

2) Co-relative data:

Baseline ACTH and total cortisol showed positive correlation to clinical severity scores (APACHE II and Lactate). They were also positively correlated to LVEF as well as vasoactive inotrope score as shown in table, all with significant P value (0.000) Table 2.

3) Comparison between survivors and non-survivors: Table 3

The mean age of survived patients was 51.3 ± 12.1 years while it was 68.9 ± 13.5 years in survivors, APACHE II was higher in non-survivors (93.9 ± 7.0 vs 67.8 ± 14.0). LVEF was lower in non survivors (26.4 ± 4.6 vs 38.0 ± 2.5) with significant P value 0.000.

Baseline ACTH was significantly lower in survivors (28.1 ± 9 vs 952.0 ± 21.3) p value: 0.000.

Baseline serum cortisol level was significantly lower in survivors 30.6 ± 6.1 vs 45.0 ± 16.3) p value: 0.000.

TC 60 min post SST was significantly lower in survivors 44.3 ± 5.4 vs 53.5 ± 9 than non survivors p value 0.001 but ΔMax TC (difference of cortisol level before and after SST) (13.8 ± 3.8 vs 8.5 ± 4.4) p value 0.000.

Serum lactate level was lower in survivors with significance: p value: 0.000.

Table 1. The baseline characteristics of the study group.

	Mean ± SD	Confidence interval 95%
Age		56.9 - 63.4
APACHE II	80.8 ± 17.1	77.3 - 84.4
LVEF%	32.2 ± 6.9	30.8 - 33.7
ACTH baseline ng/L	40.1 ± 20.4	35.8 - 44.3
Total cortisol bl ug/dl	37.8 ± 14.2	34.8 - 40.7
TC 60 min post SST	48.9 ± 12.9	46.2 - 51.6
Δmax TC	11.1 ± 4.9	10.1 - 12.2
Steroid replacement	12 (13.3%)	
Lactate	7.3 ± 2.8	6.8 - 7.9
Arterial PH	7.3 ± 0.1	7.2 - 7.3
PO2/Fio2	174.5 ± 57.8	162.4 - 186.6
MAP	57.9 ± 5.3	56.8 - 59.0
HR	102.1 ± 19.2	98.0 - 106.1
Troponin peak ng/ml	50.0 ± 27.7	44.2 - 55.8
Creatinine	5.0 ± 18.1	1.2 - 8.8
Intra-aortic balloon counter pulsation	30 (33.3%)	
Cardiac arrest	42 (46.7%)	
Mortality	45 (50.0%)	

Table 2. Correlations of ACTH and total cortisol level.

		Baseline ACTH	Total cortisol
APACHE II	r value	0.691	0.583
	p value	0.000	0.000
Lactate	r value	0.713	0.556
	p value	0.000	0.000
Peak troponin	r value	0.779	0.566
	p value	0.000	0.000
LVEF%	r value	−0.750	−0.764
	p value	0.000	0.000
Cumulative vasopressor index	r value	0.585	0.462
	p value	0.000	0.000

Table 3. Comparison between survivors and non-survivors.

	Survivors No.48	Non-survivors No.42	P value
Age	51.3 ± 12.1	68.9 ± 13.5	0.000
Gender (Male)	28 (62.2%)	24 (53.3%)	0.261
APACHE II	67.8 ± 14.0	93.9 ± 7.0	0.000
LVEF%	38.0 ± 2.5	26.4 ± 4.6	0.000
Fluid balance day 1	−89.3 ± 285.4	1459.8 ± 618.9	0.000
ACTH baseline ng/L	28.1 ± 9.9	52.0 ± 21.3	0.000
total cortisol bl ug/dl	30.6 ± 6.1	45.0 ± 16.3	0.000
TC 60 min post SST	44.3 ± 5.4	53.5 ± 16.2	0.001
Δmax TC	13.8 ± 3.8	8.5 ± 4.4	0.000
Lactate	4.9 ± 1.8	9.7 ± 0.6	0.000
Arterial PH	7.3 ± 0.1	7.2 ± 0.0	0.000
PO2/Fio2	220.6 ± 32.8	128.5 ± 36.7	0.000
MAP	62.3 ± 3.1	53.5 ± 2.7	0.000
HR	96.6 ± 7.9	107.5 ± 25.0	0.008
BMI	29.9 ± 4.5	32.3 ± 4.7	0.012
Troponin peak ng/ml	27.1 ± 17.4	73.0 ± 13.1	0.000
Creatinine	8.0 ± 25.4	1.9 ± 0.2	0.114
Epinephrine	0.1 ± 0.1	0.3 ± 0.0	0.000
Norepinephrine	0.1 ± 0.2	0.3 ± 0.0	0.000
Dopamine	4.2 ± 1.8	10.0 ± 0.0	0.000
Dobutamine	0.7 ± 1.7	6.7 ± 3.5	0.000
Inotrope score	11.5 ± 11.7	46.7 ± 3.5	0.000
Vasoactive inotropic score	23.5 ± 32.9	76.7 ± 3.5	0.000
Cumulative vasopressor index	4.8 ± 2.6	10.0 ± 0.0	0.000
IABP	6 (13.3%)	24 (53.3%)	0.000
Cardiac arrest	9 (20.0%)	33 (73.3%)	0.000

PH was higher in survivors with significant p value; 0.000.

The Oxygenation index was higher in s in survivors with significant p value; 0.000.

The MAP was higher in survivors with significant p value; 0.000.

The HR was lower in survivors with significant p value; 0.000.

The BMI was lower in survivors with significant p value; 0.008.

The peak troponin level was lower in survivors with significant p value; 0.000.

The vasoactive score was lower in survivors with significant p value; 0.000.

6 patients (13.3% of the survivors) required IABP while it inserted for 24 patients (53.3% only of non survivors) with significant p value; 0.000.

9 patients (20.0% of survivors) suffered from cardiac arrest while 33 patients (73.3% of non survivors) suffered from cardiac arrest before death p value 0.000.

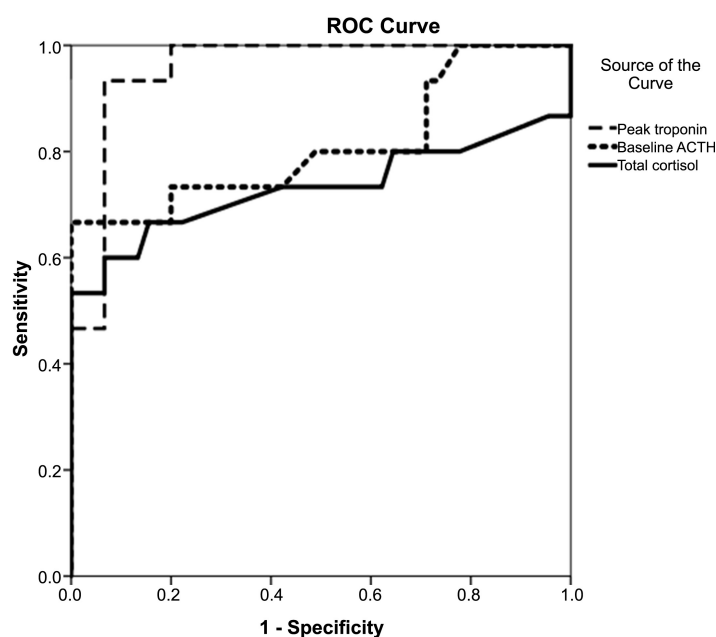### 4) The ROC curve of the peak troponin, basal cortisol and ACTH level: Figure 2 and Table 4

The area under the curve for peak troponin was 0.956 and cut off level was 50 µg/mL with sensitivity and specificity of 93.3%. The positive predictive value is 93.3% and the negative predictive value is 93.3%.

The area under the curve for ACTH was 0.811 and cut off level was 35 µg/mL with sensitivity and specificity of 73.3%. The positive predictive value is 73.3 % and the negative predictive value is 73.3%.

The area under the curve for total cortisol was 0.731 and cut off level was 35 µg/mL with sensitivity 64.3% and specificity of 86.7%. The positive predictive value is 81.7% and the negative predictive value is 72.2% (Table 4).

5) The ROC curve of the cumulative vasopressor index, inotropic score and vasoactive inotropic score Figure 3 and Table 5:


Figure 2. The ROC curve of peak troponin, basal cortisol and ACTH level in the study groups.

Table 4. Data of the ROC curve of peak troponin, ACTH and total cortisol in the study group.

	Area	p value	Cut-off	Sensitivity	Specificity	PPV	NPV
Peak troponin	0.956	0.000	50.0	93.3%	93.3%	93.3%	93.3%
ACTH	0.811	0.000	35.0	73.3%	73.3%	73.3%	73.3%
Total cortisol	0.731	0.000	35.0	64.3%	86.7%	81.8%	72.2%

Table 5. Data of the ROC curve of inotrope score, ACTH and total cortisol in the study group.

	Area	p value	Cut-off	Sensitivity	Specificity	PPV	NPV
Inotrope score	0.978	0.000	35	100.0%	93.3%	93.8%	100.0%
VIS	0.996	0.000	65	100.0%	93.3%	93.8%	100.0%
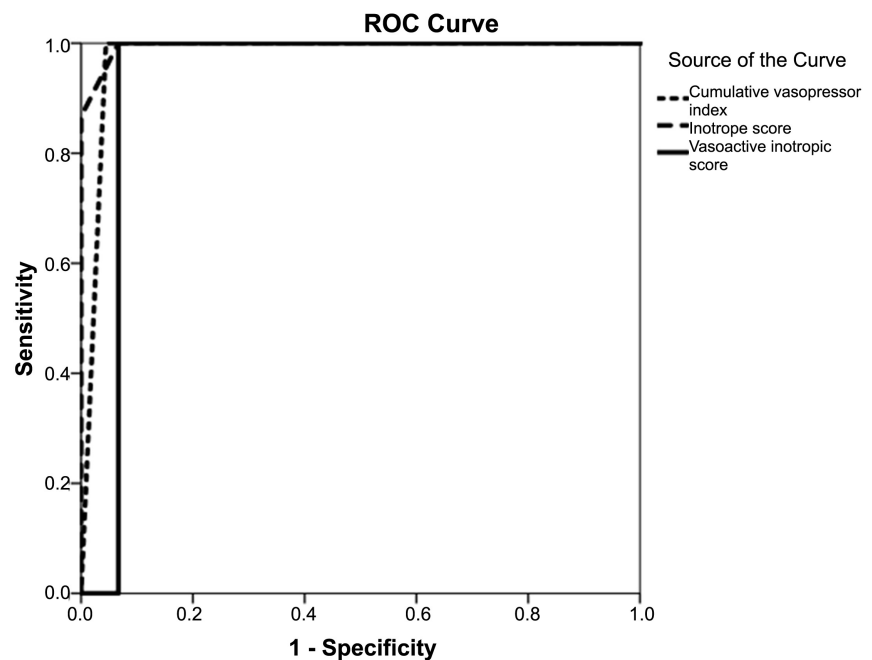
Figure 3. The ROC curve of the cumulative vasopressor index, inotropic score and vasoactive inotropic score.

The area under the curve for inotrope score was 0.978 and cut off level was 35 with sensitivity 100% and specificity of 93.3%. The positive predictive value is 93.8% and the negative predictive value is 100%

The area under the curve for vasopressor index score was 0.996 and cut off level was 65 with sensitivity 100% and specificity of 93.3%. The positive predictive value is 93.8% and the negative predictive value is 100% (Table 5).

4. Discussion

The objective of this study was to determine the prevalence of relative adrenal insufficiency by using SST in patients with cardiogenic shock complicating acute

ST-segment elevation MI.

There was a higher prevalence of cardiogenic shock in males this may be due to The higher prevalence of myocardial infarction (MI) in men in all age-specific groups than women as documented by Joshua *et al.* 2018 [5].

In this study serum total cortisol level was measured on admission and short stimulation test was done by injection of 250 micrograms ACTH (Synacthen) and another sample of cortisol level was assessed 60 minutes later. The baseline TC was 37.8 ± 14.2 μg/dL basal ACTH was 40.1 ± 20.4 ng/L and cortisol level after 60 minutes was 48.9 ± 12.9 μg/dL, these results were near to the results of Tol M.M. *et al.* who found baseline total cortisol level 34 μg/dL and 45 μg/dL [5] [6].

The study concluded that the baseline total cortisol and ACTH were correlated with APACHE II score, serum lactate, peak troponin, LVEF, inotropic index and cumulative vasoactive index with significant P value, This results are matched with the results of Ming-Hung Tsa [7] who found that the baseline total cortisol was correlated with APACHE II score and lactate level in patients diagnosed to have septic shock, Critical illness is accompanied by the activation of the hypothalamic-pituitary-adrenal axis, which is highlighted by increased serum corticotropin and cortisol levels [7] [8]. The activation of the hypothalamic-pituitary-adrenal axis is a crucial component of the host's adaptation to severe stress. Cortisol is essential for the normal function of the immune system and various cellular functions. Recently, the concept of critical illness-related corticosteroid insufficiency (CIRCI) has been put forward to describe a subnormal adrenal response to adrenocorticotropin in severe illness, in which the cortisol levels, although high in terms of absolute value, are inadequate to control the inflammatory situation [8]. The short corticotropin stimulation test (SST) is most commonly used to evaluate the appropriateness of the adrenal response in this setting [9].

In this study, APACHE II score, serum lactate, total cortisol level, peak troponin and delta max [Δmax] in cortisol levels between T0 and the highest value at T60 were associated with poor prognosis and higher mortality Maneesha, M. *et al.* [5] performed a short corticotropin stimulation test in 35 patients with cardiogenic shock after AMI by injecting of 250 μg of tetracosactrin (Synacthen) intravenously. Blood samples were obtained at baseline (T0) before and at 60 (T60) minutes after the test to determine total plasma cortisol (TC) and free cortisol concentrations. The primary outcome measure was in-hospital mortality and its association with T0 TC and maximum response to corticotropin (maximum difference [Δmax] in cortisol levels between T0 and its value at T60). The in-hospital mortality was 37%, and there was some evidence of an increased mortality in patients with T0 TC concentrations more than 34 μg/dL (p = 0.07). Maximum difference by was not an independent predictor of death. Patients with a T0 TC less than 34 μg/dL or with Δmax greater than 9 μg/dL had the most favorable survival.

In tour study the in hospital mortality was 50% the higher mortality in our

study may be due to larger sample and more extensive myocardial injury as manifested by low ejection fraction.

The study also concluded that cardiac troponin had the highest sensitivity and specificity for diagnosis of cardiogenic shock, Area under the curve is 0.978. Sensitivity is 100% and specificity is 93.3%, the same results were also concluded by a study done by Dong-Ryeol Ryu [10] who stated that Receiver operator characteristic (ROC) curve of cardiac troponin T (cTnT) for diagnosing acute myocardial infarction. The area under the curve (AUC) was 0.98 (p < 0.001; 95% CI, 0.95 - 1.00). The cTnT value of 0.35 ng/mL offers the best sensitivity and specificity; the sensitivity was 0.95 and the specificity was 0.97.

The ROC for ACTH and baseline cortisol levels were 0.811 and 0.731 respectively, There were various criteria used to diagnose adrenal insufficiency in previous studies. However, those studies were conducted in critically ill patients, and none has been done on cardiogenic shock patients so far. In this respect, the cut-off cortisol level which indicates adrenal insufficiency in severely-ill patients is still debatable [11].

Cardiogenic shock shares immune mechanisms with septic shock. Low-flow state and general inflammation causes endothelial injury and organ dysfunctions Inflammatory mediators, oxidant stress, and causes vasodilatation and low general resistance determined in several patients with cardiogenic shock complicating acute MI. Excessive oxidative stress as in septic shock has been known to suppress steroidogenesis in adrenal glands this might justify why the adrenal responsiveness is altered within the majority of patients with severe cardiogenic shock [12].

5. Conclusion

A high baseline plasma TC was associated with increased mortality in patients with cardiogenic shock post-AMI. Patients with lower baseline TC, but with a better adrenal response, appeared to have a survival benefit.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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