Journal of Cardiovascular and Thoracic Research, 2012, 4(4), 107-111
doi: 10.5681/jcvtr.2012.026
http://jcvtr.tbzmed.ac.ir

Serum Cortisol Levels as a Predictor of Neurologic Survival in Successfully Resuscitated Victims of Cardiopulmonary Arrest

Nader Tavakoli[1], Ali Bidari[2], Samad Shams Vahdati[3*]

[1]*Department of Emergency Medicine, Hazrate-Rasul Hospital ,Tehran University of Medical Science, Tehran, Iran*
[2]*Department of Emergency Medicine, Sina Hospital ,Tehran University of Medical Science, Tehran, Iran*
[3]*Department of Emergency Medicine, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 3 June 2012
Accepted: 8 Oct 2012
ePublished: 30 Oct 2012

Keywords:
Cardiopulmonary Arrest
Cortisol Level
Neurologic Outcome

ABSTRACT

Introduction: Out-of-hospital cardiac arrest (OHCA) is the most stressful lifetime event for the victims and an important issue for the emergency physicians. The status of the hypothalamic pituitary- adrenal axis (HPA) function in successfully resuscitated victims of cardiopulmonary arrest has been recently of an interest for the researchers. **Methods**: In a prospective cohort study, 50 successfully resuscitated OHCA victims' serum cortisol levels were measured 5 minutes and 1 hour after return of spontaneous circulation (ROSC). The data were analyzed comparing the one-week neurologic survival. **Results**: Fifty blood samples were obtained for serum cortisol levels after 5 minutes of ROSC. Fourteen patients (28%) pronounced death during one hour after CPR. Blood sample from living 36 patients after one hour post-CPR were obtained for second cortisol assay. Eleven patients (22%) were neurologically survived after one week. Seven patients (14%) were discharged finally from hospital with good neurologic recovery. The serum cortisol levels in both the neurologically surviving and the non-surviving after 5 minutes of ROSC patients were 63.4 ±13.6 and 43.2±25.5(microg/ml), (mean±S.D., respectively) and after 1 hour of ROSC patients' serum cortisol levels were 64.9±13.1 and 47.3±27.1(microg/ml), (mean±S.D., respectively). The difference was significantly higher in neurologically survived group in both 5 minutes and 1 hour after ROSC (P= 0.015 and 0.013 respectively). **Conclusion**: serum cortisol levels after 5 minutes and one hour of ROSC in victims of cardiopulmonary arrest are significantly higher in neurologically survived than non-survived patients.

Introduction

Stress from many various sources including cold, infection, trauma, etc and other disturbances to homeostasis stimulate the hypothalamic pituitary-adrenal (HPA) axis, increasing factor of six and in the continue cortisol level that is related to the severity of the illness leading to decrease in the normal regulation of these hormones.[1-4] There is increasing evidence of HPA insufficiency in critically ill patients, by circulating suppressive factors which are released throughout the systemic inflammation.[4-14]

Cardiopulmonary arrest (CPA) is considered the most stressful lifetime event is.[1] Out-of-hospital cardiac arrest (OHCA) is an important issue for the emergency physicians, accounting for 250,000 deaths per year in the United States and Canada, with death rates ranging from 4% to 33%.[6,7] Many stress hormones could be released during CPA. Elevated serum cortisol concentrations, positively correlating with the severity of illness and negatively with the survival, can be seen in patients with severe illness.[1]

Despite progresses achieved in resuscitation programs, survival following out-of-hospital cardiac arrest (OHCA) remains low. Less than one third of cardiopulmonary resuscitation (CPR) attempts started out of hospitals result in restoration of spontaneous circulation.[15,16]

Nowadays, status of HPA axis function in successful resuscitation of cardiopulmonary arrest has become the center of attention for most researchers; however, these studies performed in this regard are few and of low sample sizes.[1,5,9,12] Post-resuscitation abnormalities are similar to sever sepsis and mimic its immunologic and coagulation disorders thus therapeutic approaches recently used with success in severe sepsis may be effective in patients successfully resuscitated after cardiac arrest.[16]

Therefore, we decided to evaluate the status of HPA axis function by serum cortisol assay in victims of OHCA or immediately after arrival to emergency department shortly after return of ROSC. Results were analyzed in relation to the neurologic outcome, survival and hospital discharge of patients.

***Corresponding author:** Samad Shams Vahdati , E-mail: sshamsv@yahoo.com

Materials and methods

Study design, patients population and data collection

This prospective cohort study was performed in the first academic emergency department (ED) of Hazrat-e-Rasool general hospital Tehran, Iran starting from October 2009 with a target sample size of fifty. Enrollment phase terminated in March 2011. All patients experienced CPA in the pre-hospital setting or immediately after arrival in the ED provided that they were successfully resuscitated to the point that ROSC was maintained as the indicator of successful resuscitation for at least five minutes.

The patients were resuscitated by emergency medicine residents or attending physicians according to advanced cardiac life support (ACLS; American Heart Association Guideline 2005) protocol in ED and ROSCE was confirmed by emergency medicine residents or attending physicians. We excluded all patients younger than 18 years of age, pregnant, taking corticosteroid within one month prior to their referral and cases in which traumatic injury or terminal illness was responsible for CPA.

Blood samples were collected for total serum cortisol assay by emergency physician at five and sixty minutes following ROSC. The latter was applicable only if ROSC had been maintained. The reason for recheck samples collection after sixty minutes of ROSC was to provide enough time to observe cortisol increase following being exposed to a stressful event. Patients were categorized into neurologic survival group who left responsive, with some disabilities or gained good neurologic recovery at one week of ROSC. All who died or remained unresponsive in less than one week following study enrollment were categorized as neurologic non-survival group.

The blood samples for cortisol assay were collected in polystyrene tube either not containing any additive or containing heparin or EDTA. Serum was separated immediately after collection from cells with centrifugation and kept frozen in -20 degrees centigrade until analysis.

The serum cortisol levels were measured by radioimmunoassay (Cortisol-RIA, Immunotech kit, Beckman Coulter Inc., Prague, Czech Republic) with analytical sensitivity of 10 nM (nanomol) and normal range between 9.0 and 26.0 microg/dl. If samples had concentrations more than the highest calibrator, they were diluted in the zero calibrator.

The clinical parameters (the vital signs and neurologic recovery) were followed until the patients expired, survived and/or discharged from the hospital. The levels of consciousness were documented according to AVPU scale (Alert, Verbal, Painful and Unresponsive).

The study received approval from medical standard committee of medical school and institutional ethics committee of the hospital.

Statistical analysis

Univariate analyses were performed using the Mann-Whitney test for continuous variables and chi-squared or Fisher's exact test where appropriate for categorical variables. All data were expressed as the mean ±standard deviation (S.D.). Recorded variables were age (years), gender (male, female), duration of hospital admission (days), outcome (survived or expired), level of consciousness (APVU) and systolic and diastolic blood pressure (mmHg) after one week, time of arrest (hour), the causes of CPA, levels of cortisol (microg/dl) at fifth minute and first hour after ROSC.

Correlation between the cortisol levels with neurologic survival and hospital discharge of patients was analyzed by a linear regression analysis (Pearson's Method). A *P*-value less than 0.05 was regarded as significant.

Multivariate analyses were performed using a logistic regression model with a stepwise selection procedure to select the variables. All statistical analyses were performed using SPSS software (version 15.0).

Results

Fifty patients were enrolled in this study. The oldest and youngest patients were 85 and 20 years old respectively. Fourteen patients (28%) expired during one hour after CPR. Blood samples from 36 survived patients after one hour post-CPR were obtained for second cortisol assay. Thirty-three patients (64%) pronounced death during 24 hours after CPR. Eleven patients (22%) were neurologically survived after one week. Seven patients (14%) were finally discharged from hospital with good neurologic recovery (Table 1 and 2).

Table 1. Characteristics of patients in neurologically survived and non-survived patients Patient's characteristics (N=50)

Neurologic survival after one week			
	Non-survived	Survived	P value
Sex (male: female)	22:17	5:6	0.733
Age (years-old)	62.7 (17.7)	62.1 (14.8)	0.922
Etiology			0.129
Cardiac	15	9	
Non-cardiac	24	2	
Serum cortisol levels (5min ; microg/ml)	43.2 (25.5)	63.4 (13.6)	0.015
Serum cortisol levels (1hour; microg/ml)	47.3(27.1)	64.9(13.1)	0.013
Data are shown as the means (SD), Significant *P*- Value < 0.05			

Table 2. characteristic of patients in discharged and expired group Patient's characteristics (N=50)

Hospital discharge			
	Expired *N*: 43	Discharged *N*: 7	P value
Sex (male: female)	23:20	4:3	0.593
Age (years-old)	62.8 (17.4)	60.9(14.4)	0.780
Etiology			0.423
Cardiac	17	7	
Non-cardiac	26	0	
Serum cortisol levels (5min ; microg/ml)	45.9 (25.7)	58.6 (14.4)	0.212
Serum cortisol levels (1hour; microg/ml)	50.1(26.6)	61.3(14.6)	0.166
Data are shown as the means (SD), Significant *P*- Value < 0.05			

There were significant differences, however, between these two groups regarding serum cortisol level in five minutes and one hour after ROSC (P= 0.015 and 0.013 respectively). There were no significant differences between these two groups with respect to gender, age and etiology of CPA. There were no significant differences in serum cortisol levels 5 minutes and 1 hour after ROSC between the patients discharged from hospital with good neurologic recovery and the ones who ultimately died (Table 2; Table 3).

Table 3. The serum cortisol levels 5minutes and 1hour of ROSC according to the etiology of CPA

	Serum cortisol after 5 minutes (microg/ml) N=50,sig.=0.175	Serum cortisol after 1 hour (microg/ml) N=36,sig=0.216
Cardiac	43.9 (19.0)	49.2 (22.1)
Cerebral	39.5 (18.0)	40.9 (16.2)
Pulmonary	69.7 (27.6)	65.1 (23.6)
Others	59.7 (34.8)	55.4 (34.9)
Unknown	45.4 (31.7)	83.4 (31.1)

Data are shown as the means (SD), Significant *P*- Value < 0.05

Discussion

Increase in serum cortisol level over the upper limit of normal range is observed in most patients even only five minutes of ROSC. Two groups of patients (survived and non-survived) were comparable regarding demographic parameters. There were significant differences, however, between these two groups regarding serum cortisol level in five minutes and one hour after ROSC. There were no significant differences between these two groups with respect to gender, age, etiology of CPA, time of arrest. There were no significant differences in serum cortisol levels 5 minutes and 1 hour after ROSC between the patients discharged from hospital with good neurologic recovery with who ultimately died.

The role of serum cortisol level in outcome of successfully resuscitated victims of CPA and analysis of the relationship between stress hormones and outcome of patients has been shown in animal experiences.[7]

Our study suggests that serum cortisol levels may serve as a predictor of survival in successfully resuscitated victims of CPA. Ischemia occurring during CPA can lead to adrenal insufficiency in the post-CPR state. Reperfusion injury in patients resuscitated after CPA is well-known to subsequently damage organs. Organ damage due to reperfusion injury may influence the outcome after resuscitation. The serum interleukin-8 (IL-8) levels in patients who died or became brain dead within 1 week after ROSC were significantly higher than those in other patients.[1,17] The serum IL-8 is a predictor of unfavorable neurological course in CPA.[1,18] The high level of IL-8 in the resuscitated CPA cases may induce organ damage, especially brain damage due to reperfusion injury. The neuroendocrine and immune systems are interconnected with pathways available for reciprocal regulation. Following exposure to proinflammatory cytokines such as IL-8, the HPA axis is stimulated to release ACTH from the pituitary gland and cortisol from the adrenal gland.[1]

Hydrocortisone inhibits lipopolysaccharide-induced IL-8 production by human whole blood.[1,19] Cytokines stimulate ACTH, and ACTH in turns stimulates cortisol inhibiting cytokines. Subsequently, these hormones can down regulate the immune responses. Cortisol might have an anti-inflammatory effect including the inhibition of the cytokine network effect and also a protective effect against organ damage based on reperfusion injury.[1]

The low cardiac output during prolonged CPR may lead to dysfunction of HPA because of ischemic injury; thus, it may be manifested as inability to increase cortisol secretion. This low cortisol level supposed to be reason of organ damage by reperfusion injury.[1]

The recovery of spontaneous circulation leads to a whole-body ischemia-reperfusion syndrome designated as "postresuscitation disease"[6,20] and resembling severe sepsis.[6] Inflammation and coagulopathy are seen after successful circulatory arrest resuscitation.[6,21-23]

This suggests that therapeutic approaches used recently with success in severe sepsis should be investigated in patients successfully resuscitated after cardiac arrest.[16] In animal experiments, a higher rate of return for spontaneous circulation after the administration of vasopressin has been reported than after the administration of epinephrine (adrenaline). A study demonstrated that the administration of ACTH might be a significantly beneficial therapeutic approach for victims of cardiac arrest.[1,10,11] The exogenous administration of cortisol in patients resuscitated after CPA might prevent the organs from damage due to reperfusion injury and eliminate the outcome of the resuscitated patients. Jastremski and co-workers[24,25] reported that cortisol treatment did not improve neurological recovery following cardiac arrest. In their reports, cortisol administration was within 2.7 h and within 8 h after ROSC.[24,25]

Adrenal insufficiency as assessed by corticotrophin test is common after cardiac arrest as same as septic shock but there is not any relation with severity. The lower cortisol levels in patients with early refractory shock are suggestive of relative adrenal insufficiency.[1]

Limitations

Our study had several limitations. The small sample size (n = 50) and high mortality rate (86%) did not allow us to provide a reliable interpretation regarding mortality. We did not perform ACTH stimulation test as a standard tool to evaluate adrenal insufficiency to stress. Yet, we believed that the extreme stress of circulatory collapse in arrested victims would be a powerful stimulus to release cortisol from adrenals.

We were unable to show a cause and effect relationship

between initial serum cortisol level and patient outcome. One may postulate the more powerful adrenal response to circulatory collapse may only be surrogate marker of less multi-system damage due to inciting event. Experimental animal studies have suggested that stress dose hydrocortisone may be beneficial to post-CPR victims. The fact is in favor of causal effect of serum cortisol on survival outcome.[7] Large multi-centric studies are however required to explore the issue.

This study is unique among humanistic studies and had the advantages over earlier rare similar published studies in the literature[1], because of the greater sample size. Serial serum cortisol assay (immediately and one hour after successful CPR) provides more reliable assessment on the status of HPA axis in this special group of the patients. We tried to recruit patients into the study using strict inclusion criteria. Our purpose was to provide a relatively more homogenous patient population and to avoid confounding variables.

Definitions of adrenal dysfunction in post- resuscitation disease need to be developed in larger studies.[6] Our data shows that serum cortisol levels on admission can predict the outcome of patients resuscitated after CPA. The earlier the cortisol is administered on admission, the more positive the therapeutic effect; this would help to improve the outcome of patients resuscitated. Further studies will be undertaken to clarify whether earlier administration of cortisol on admission could improve the outcome of patients resuscitated after CPA.[1]

Conclusion

Serum cortisol levels after 5 minutes and one hour of ROSC in victims of CPA are significantly higher in neurologically survived than non-survival patients.

Conflict of interests: The authors declare no conflicts of interest.

References

1. Ito T, Saitoh D, Takasu A, Kiyozumi T, Sakamoto T, Okada Y. Serum cortisol as a predictive marker of the outcome in patients resuscitated after cardiopulmonary arrest. **Resuscitation** 2004;62:55-60.

2. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. **N Engl J Med** 2004;350:1629-38.

3. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. **N Engl J Med** 2003;348:727-34.

4. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. **Chest** 2002;122:1784-96.

5. Pene F, Hyvernat H, Mallet V, Cariou A, Carli P, Spaulding C, et al. Prognostic value of relative adrenal insufficiency after out-of-hospital cardiac arrest. **Intensive Care Med** 2005;31:627-33.

6. Hekimian G, Baugnon T, Thuong M, Monchi M, Dabbane H, Jaby D, et al. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. **Shock** 2004; 22:116-9.

7. Hydrocortisone in Patients of Out-of-Hospital Cardiac Arrest [homepage on the Internet].USA: NIH;[cited 2011 Oct 15]. Available from: http://clinicaltrials.gov/ct2/show/NCT00172354

8. Schultz CH, Rivers EP, Feldkamp CS, Goad EG, Smithline HA, Martin GB, et al. A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest. **Crit Care Med** 1993;21:1339-47.

9. Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency. **Crit Care Clin** 2001;17:25-41.

10. Smithline H, Rivers E, Appleton T, Nowak R. Corticosteroid supplementation during cardiac arrest in rats. **Resuscitation** 1993; 25:257-64.

11. Foley PJ, Tacker WA, Wortsman J, Frank S, Cryer PE. Plasma catecholamine and serum cortisol responses to experimental cardiac arrest in dogs. **Am J Physiol** 1987; 253:E283-9.

12. Rydvall A, Brandstrom AK, Banga R, Asplund K, Backlund U, Stegmayr BG. Plasma cortisol is often decreased in patients treated in an intensive care unit. **Intensive Care Med** 2000;26:545-51.

13. Moran JL, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P. Hypocortisolaemia and adrenocortical responsiveness at onset of septic shock. **Intensive Care Med** 1994;20:489-95.

14. Goodman S, Sprung CL. The International Sepsis Forum's controversies in sepsis: corticosteroids should be used to treat septic shock. **Crit Care** 2002;6:381-3.

15. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. **N Engl J Med** 2002;346:557-63.

16. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. **J Am Coll Cardiol** 2002;40:2110-6.

17. Ito T, Saitoh D, Fukuzuka K, Kiyozumi T, Kawakami M, Sakamoto T, et al. Significance of elevated serum interleukin-8 in patients resuscitated after cardiopulmonary arrest. **Resuscitation** 2001; 51:47-53.

18. Ito T, Saitoh D, Takasu A, Norio H, Kiyozumi T, Sakamoto T, et al. Serum interleukin-8 as a predictive marker for a comparative neurologic outcome analysis of patients resuscitated after cardiopulmonary arrest. **Crit Care Med** 2003;31:2415-6.

19. van der Poll T, Lowry SF. Lipopolysaccharide-induced interleukin 8 production by human whole blood is enhanced by epinephrine and inhibited by hydrocortisone. **Infect Immun** 1997;65:2378-81.

20. Negovsky VA, Gurvitch AM. Post-resuscitation disease--a new nosological entity. Its reality and significance. **Resuscitation** 1995;30:23-7.

21. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. **Circulation** 2002;106:562-8.

22. Adrie C, Laurent I, Joly LM, Vinsonneau C, Fraisse F, Um S, et al. Depletion of proteins C-S and antithrombin after successful cardiopulmonary resuscitation (CPR). **Intensive Care Med** 2002; 100:381.

23. Bottiger BW, Motsch J, Bohrer H, Boker T, Aulmann M, Nawroth PP, et al. Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. **Circulation** 1995;92:2572-8.
24. Jastremski M, Sutton-Tyrrell K, Vaagenes P, Abramson N, Heiselman D, Safar P. Glucocorticoid treatment does not improve neurological recovery following cardiac arrest. Brain Resuscitation Clinical Trial I Study Group. **JAMA** 1989;262:3427-30.
25. Grafton ST, Longstreth WT Jr. Steroids after cardiac arrest: a retrospective study with concurrent, nonrandomized controls. **Neurology** 1988;38:1315-6.