Association between oxidative stress index and post-CPR early mortality in cardiac arrest patients: A prospective observational study

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Abstract

Objective: Cardiopulmonary resuscitation (CPR) is a series of lifesaving actions that improve the chance of survival following cardiac arrest (CA). Many clinical and laboratory parameters, such as the presence of asystole, out-of-hospital CPR, and duration of cardiac arrest, are associated with failed CPR in patients with CA. Asystole is a state of no cardiac electrical activity, along with the absence of contractions of the myocardium and absence of cardiac output. Oxidative stress index (OSI), which is the ratio of total oxidative status to total antioxidant status, increases by ischemia-reperfusion injury. We investigated whether OSI levels in patients with CA could predict early mortality after CPR.

Methods: This study has a prospective observational cohort design. Five patients with a history of cancer, four patients who developed hemolysis in their blood, six patients who were transferred to our hospital from other hospitals, and six patients in whom blood samples for OSI could not be stored properly were excluded. Finally, a total of 90 in-hospital or out-of-hospital CA patients and 40 age- and sex-matched healthy volunteers as the control group were evaluated prospectively. The patients were classified according to the CPR response into a successful group (n=46) and a failed group (n=44). Comparisons between groups were performed using one-way ANOVA with post hoc analysis by Tukey's HSD or independent samples t-test and the Kruskal-Wallis tests or Mann- Whitney U test for normally and abnormally distributed data, respectively. Also, we used chi-square test, Spearman's correlation test, univariate and multible logistic regression analyses, and receiver operator characteristic curve analysis.

Results: OSI was 3.0±4.0, 5.6±4.3, and 8.7±3.8 in the control group, the successful CPR group, and the failed CPR group, respectively ($p<0.001$ for the 2 comparisons). OSI on admission, ischemia-modified albumin, presence of asystole, mean duration of cardiac arrest, out-of-hospital CPR, pH, and potassium and sodium levels were found to have prognostic significance in the univariate analysis. In the multivariate logistic regression model, OSI on admission (OR=1.325, p=0.003), ischemia-modified albumin (OR=1.008, p=0.005), presence of asystole (OR=13.576, $p<0.001$), and sodium level (OR=1.132, p=0.029) remained associated with an increased risk of early mortality. In addition, the optimal cut-off value of OSI to predict post-CPR mortality was measured as >6.02, with 84.1% sensitivity and 76.1% specificity.

Conclusion: Elevated OSI levels can predict failed CPR in CA patients. *(Anatol J Cardiol 2015; 15: 737-43)*

Keywords: cardiopulmonary resuscitation, oxidative stress index, cardiac arrest

Introduction

Oxidative stress occurs if the quantity of free radicals exceeds the capacity of the endogenous antioxidant defense mechanism (1, 2). The ratio of total oxidant status/total antioxidant status was named the oxidative stress index (OSI) as an indicator of the degree of oxidative damage (3). Several studies reported that OSI is associated with endothelial dysfunction, which is a common denominator of cardiovascular disorders, such as coronary artery disease, acute myocardial infarction, metabolic syndrome, hypertension, and diabetes mellitus (4-10).

Cardiopulmonary resuscitation (CPR) is a series of lifesaving actions that improve the chance of survival following cardiac arrest. Return of spontaneous circulation from cardiac arrest (CA) is achieved in about 30%-40% of cases. Although it is known that out-of-hospital CPR and duration of cardiac arrest are associated with failed CPR, there are no valid laboratory parameters that have shown the success of CPR (11, 12).

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However, recently, we reported that increased MMP-9 levels were related to failed CPR (13).

Recent studies demonstrated that duration of CPR, time of arrest, presence of asystole, out-of-hospital CPR, poor Glasgow coma score, hemodynamic instability, and electrolyte imbalance were associated with failed CPR (14-20). In this subgroup analysis of our study, we aimed to investigate the relationship between admission OSI levels and failed CPR in CA patients, independently of the parameters mentioned above.

Methods

Study design

This study has a prospective observational cohort design.

Clinical data collection

This study is a subgroup analysis of a previously published work (13). A total of 110 in-hospital or out-of-hospital CA patients who were admitted to Cumhuriyet University Hospital the emergency department were prospectively considered for enrollment between February 2010 and March 2011. Five patients with a history of cancer, four patients who developed hemolysis in their blood, six patients who were transferred to our hospital from other hospitals, and six patients in whom blood samples for OSI could not be stored properly were excluded. For the outpatients, the history of index CA was obtained from the ambulance medical staff. Those with CPR duration of longer than 10 min inside the ambulance before getting into the emergency department (ED) were not considered for the study. The team included an emergency physician and two registered nurses or medical technicians. Finally, a total of 90 CA patients and 40 age- and sex-matched healthy volunteers as the control group were evaluated prospectively.

The study was performed in accordance with the Declaration of Helsinki for Human Research and was approved by the institutional Ethics Committee (Registry number: 2009-06/13).

Definitions

Cardiac arrest was defined as the interruption of spontaneous respiratory efforts and the absence of any palpable pulses. Successful resuscitation was defined as the return of a palpable pulse and an ECG rhythm other than ventricular fibrillation or ventricular tachycardia. Asystole is a state of no cardiac electrical activity, along with the absence of contractions of the myocardium and absence of cardiac output.

Cardiac arrest patients were classified according to the acute CPR response into a successful group (n=46, acute responders) and a failed group (n=44). The successful group was composed of patients with acute response to CPR within the emergency department, and hence, the group included those patients who were discharged from the emergency department alive. The data regarding the site and the time of CA were obtained from first-degree relatives and CPR staff. The initial electrocardiograms, obtained at admission, were recorded. The study team was initially educated on high-quality CPR according to guidelines (21), and the quality of CPR (qualitatively as poor-intermediate-good-ideal) was monitored by an independent senior emergency physician throughout the study.

Biomarker testing

Blood sampling from a venous and/or arterial line was obtained in all patients with CA. Patients in whom blood sampling could not be made within 10 min after CPR were not included in the study. Samples were stored at -80°C. The serum was separated from the cells by centrifugation at 3000 rpm for 10 min and then analyzed. Plasma total oxidant status (TOS) and total antioxidant capacity (TAS) were assessed using an automated measurement method, as described previously (22, 23).

Total oxidant status (TOS) measurement

The TOS of serum was determined using a novel automated measurement method, also developed by Erel et al. (22). The assay is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidant species in acidic medium and the measurement of the ferric ion by xylenol orange. The ferric ion makes a colored complex with xylene orange in an acidic medium. The color intensity is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide, and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L).

Total antioxidant capacity (TAC) measurement

Serum TAS was determined using a novel automated measurement method, developed by Erel et al. (23). In this method, hydroxyl radical is produced by the Fenton reaction, and it reacts with the colorless substrate O-dianisidine to produce dianisyl radical. After addition of a plasma sample, the oxidative reactions initiated by the hydroxyl radicals present in the reaction are suppressed by the antioxidant components of the plasma, preventing the color change and thereby providing an effective measurement of TAC. The assay results were expressed as mmol Trolox Eq/L.

Determination of OSI

The OSI is defined as the ratio of TOS to TAS, expressed as a percentage. For the calculation, TAS units were changed to mmol/L, and the OSI value was calculated according to the following formula: OSI (arbitrary units)=TOS (μmol H_2O_2 equivalents/L)/TAS (mmol Trolox® equivalents/L) $x10^{-1}$ (3).

Statistical analysis

Parametric data were expressed as mean±standard deviation, and categorical data were expressed as percentages. SPSS 14.0 (SPSS, Inc., Chicago, IL, USA) was used to perform the statistical procedures. Receiver operator characteristic (ROC)

Table 1. Baseline characteristics of study patients

	Control Group (n: 40)		Successful CPR (n: 46)		Failed CPR (n: 44)		*P*	
Study marker								
Oxidative stress index	3.0±4.0		5.6±4.3		8.7±3.8		<0.001	
		p<0.001		p<0.001				
Baseline characteristics								
Age, years	66±7		66±16		71±14		0.146	
Female	18 (45%)		21 (46%)		15 (34%)		0.467	
Hypertension			25 (54%)		26 (59%)		0.650	
Diabetes mellitus			11 (24%)		10 (23%)		0.894	
Coronary artery disease			29 (63%)		28 (64%)		0.953	
Chronic obstructive pulmonary disease			11 (24%)		6 (14%)		0.210	
Traditional predictors of failed CPR								
Out-of-hospital CPR			17 (37%)		29 (66%)		0.006	
Mean duration of cardiac arrest before CPR, minutes			2.7±4.1		8.7±3.8		<0.001	
First ECG rhythm								
Asystole		11 (24%)		35 (79%)		<0.001		
Electromechanical dissociation			1 (2%)		0 (0%)		1.000	
Pulseless ventricular tachycardia			2 (4%)		0 (0%)		0.495	
Laboratory analysis								
Arterial pH			7.2±0.2		7.1±2		0.058	
pO_2, (torr)			67±37		63±30		0.554	
PCO_2, (torr)			48±21		53±24		0.353	
Ischemia-modified albumin, mmol/lt			623±155		717±105		<0.001	
Bicarbonate, mmol/L			19±10		19±8		0.828	
Oxygen saturation, %			79±15		77±13		0.589	
Hemoglobin, gr/dL		12.8±2.7		13.3±2.3		0.421		
Platelet count $x10^3$		258±129		236±94		0.365		
Sodium, mEq/L			135±7		138±5		0.016	
Potassium, mEq/L		4.7±1		5.4±1.3		0.010		
Troponin, mg/dL			2.5±12		2.6±11		0.971	

CPR - cardiopulmonary resuscitation
Data are presented as number (percentage) and mean±SD values.
*One-way ANOVA with post hoc analysis by Tukey's HSD and/or Kruskal-Wallis test, independent samples t-test and/or Mann- Whitney U test, and Chi-square test

curve analysis was performed to identify the optimal cut-off point of OSI (at which the sensitivity and specificity would be maximal) for the prediction of early mortality after CPR. Area under the curve (AUC) values were calculated as measures of the accuracy of the tests. We compared the AUC with the use of the Z test. Comparisons between groups were performed using one-way ANOVA with post hoc analysis by Tukey's HSD or independent samples t-test and the Kruskal-Wallis tests or Mann-Whitney U test for normally and abnormally distributed data, respectively. The categorical variables between groups were analyzed using the chi-square test. Correlation was evaluated by the Spearman's correlation test. We used univariate logistic regression analysis to quantify the association of variables with mortality after CPR. Variables that were found to be statistically significant in the univariate analysis and other potential confounders, such as presence of diabetes mellitus, were used in a multiple logistic regression model with the forward stepwise method in order to determine the independent prognostic factors of mortality after CPR. A p value of 0.05 was considered statistically significant.

Power analysis

On the basis of the mean values of OSI (failed CPR 37, successful CPR 37, alpha degree of freedom as 0.05), the two-tailed power was 90% in the study.

Table 2. Correlation coefficients for oxidative stress index

	R	*P*
Presence of asystole	0.254	0.016
Mean duration of cardiac arrest, minutes	0.391	<0.001
Presence of diabetes mellitus	0.248	0.018

Results

OSI was 3.0±4.0, 5±4.3, and 8.7±3.8 in the control group, the successful CPR group, and the failed CPR group, respectively. OSI levels were observed to be significantly higher in patients with failed CPR compared to those with successful CPR and the control group (p<0.001 and p<0.001, respectively). In addition, those with successful CPR after CA were also detected to have a significantly higher OSI level relative to the control group (p<0.001) (Table 1, Fig.1).

A comparison of the baseline characteristics of the patients in the successful and failed CPR groups and the conventional risk factors for failed CPR are listed in Table 1. The presence of out-of-hospital CPR was more frequent among patients with failed CPR relative to patients with successful CPR. Also, the mean duration of CA was longer in patients with failed CPR compared with those with successful CPR. The presence of asystole at admission was more frequent in patients who died compared with those who survived after CPR. Patients with failed CPR had also significantly higher potassium and sodium levels. Although statistically insignificant, acidosis was more frequent in patients failed CPR. Furthermore, ischemia-modified albumin (IMA) levels were observed to be significantly higher in patients with failed CPR compared to those with successful CPR (p<0.001). There was no statistical difference between the two groups in baseline characteristics and the other laboratory parameters (Table 1).

OSI levels were mildly correlated with the presence of asystole (r=0.254, p=0.016) and the presence of diabetes mellitus (r=0.248, p=0.018) and moderately correlated with the mean duration of CA before initiation of CPR (r=0.391, p<0.001, Table 2). There was no significant correlation between OSI level and the other laboratory findings (p>0.05).

Results of the univariate and multivariate logistic regression analyses for early mortality are listed in Table 3. Oxidative stress index on admission, ischemia-modified albumin, presence of asystole, mean duration of cardiac arrest, out-of-hospital CPR, pH, and potassium and sodium levels were found to have prognostic significance in the univariate analysis. In the multivariate logistic regression model, OSI on admission (OR=1.325, 95% CI: 1.110-1.595, p=0.003), ischemia-modified albumin (OR=1.008, 95% CI=1.002-1.014, p=0.005), presence of asystole (OR=13.576, 95% CI=3.867-47.667, p<0.001), and sodium level (OR=1.132 95% CI=1.013-1.264, p=0.029) remained associated with an increased risk of early mortality after adjustment of other potential confounders (presence of diabetes mellitus) and variables found to be statistically significant in the univariate analysis (Table 3).

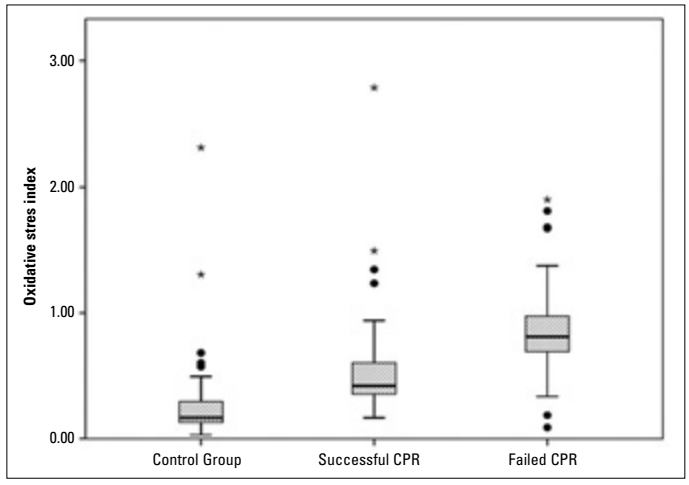

Figure 1. Comparison of oxidative stress index levels between the three groups

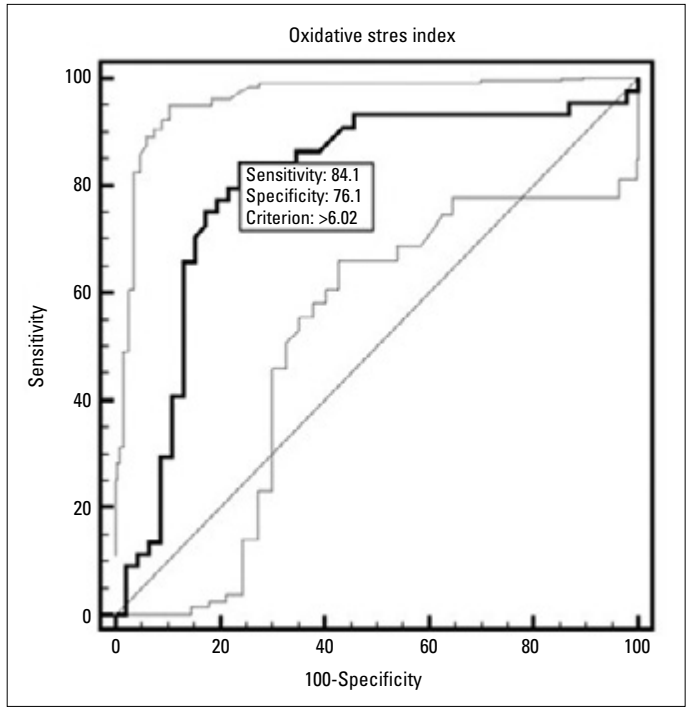

Figure 2. ROC curve for oxidative stress index to predict mortality after cardiopulmonary resuscitation (CPR) (EAA 0.800, 95% CI- 0.703-0.877)

According to the ROC curve analysis, the optimal cut-off value of OSI to predict post-CPR mortality was measured as >6.02, with 84.1% sensitivity and 76.1% specificity (AUC 0.800, 95% CI: 0.703-0.877, Fig. 2).

Discussion

To the best of our knowledge, for the first time in the literature, we showed that OSI levels are significantly increased in CA patients. Moreover, elevated OSI levels are correlated with worse clinical parameters, such as presence of asystole, diabetes mellitus, and mean duration of cardiac arrest. Finally, even after controlling these parameters, we found that higher OSI

Table 3. Univariate and multivariate analyses of mortality after CPR

	Univariate			Multiple		
Variable	***P***	**OR**	**(95% CI)**	***P***	**OR**	**(95% CI)**
Oxidative stress index	0.002	1.249	1.084-1.439	0.003	1.325	1.110-1.595
Ischemia-modified albumin, mmol/Lt	0.002	1.006	1.002-1.009	0.005	1.008	1.002-1.014
Presence of asystole	<0.001	12.374	4.562-33.561	<0.001	13.576	3.867-47.667
Mean duration of cardiac arrest	<0.001	1.254	1.135-1.385			
Out-of-hospital CPR	0.007	3.298	1.390-7.827			
Potassium, mEq/L	0.014	1.623	1.101-2.392			
Sodium, mEq/L	0.025	1.096	1.012-1.188	0.029	1.132	1.013-1.264
pH	0.062	0.110	0.011-1.115			
Presence of diabetes mellitus	0.894	1.069	0.402-2.841			

All variables from Table 1 were examined, and only those significant at a *P*<0.1 level and those with a correlated OSI level are shown in the univariate analysis. The multiple logistic regression model included all univariate predictors and those with correlating with OSI level. CI - confidence interval; OR - odds ratio; CPR - cardiopulmonary resuscitation

levels were a strongly independent predictor of failed CPR. Also, IMA and sodium levels were increased in CA patients and observed to be significantly higher in the failed CPR group compared with those with successful CPR.

Previous studies demonstrated that duration of CPR, time of arrest, presence of asystole, out-of-hospital CPR, poor Glasgow coma score, hemodynamic instability, and electrolyte imbalance are associated with failed CPR (14-20). Whereas biomarker-based strategy could also be useful to predict acute CPR success, it has not been used in the decision-making of when to end CPR or faith of CPR. Some trials have reported that biomarkers, such as neuron-specific enolase, S-100, IMA, and some adhesion molecules, could also be beneficial, in addition to prognostic assessment based on clinical observation (24-27). In addition, Rosen et al. (28) recently found that the marked increase in CSF levels of neurofilament light protein (NFL) and total tau (T-tau) was significantly higher in patients with a poor outcome after CA. Finally, Annborn et al. (29) determined that concentrations of C-terminal provasopressin (CT-proAVP or copeptin), the cardiac biomarker MR-proANP, and peroxiredoxin 4 (Prx4), a biomarker of oxidation injury, are significantly higher in patients with failed CPR. Hence, it is considered that this outcome was potentially driven by CA-related oxidative stress and CPR-related ischemia-reperfusion injury.

Reactive oxygen species (ROS) are the most common radicals in human biological cells. ROS are widely recognized as important mediators of cell growth, adhesion, differentiation, senescence, and apoptosis. Oxidative stress occurs when intracellular concentrations of free radicals increase over the physiological values. Mammalian cells actuate enzymatic and nonenzymatic antioxidant defense systems to prevent oxidative damage. The ratio of TOS to TAC represents the OSI (30, 31). Several studies have shown that elevated OSI level is associated with inflammatory bowel disease, pemphigus vulgaris, Crimean-Congo hemorrhagic fever, essential thrombocythemia, and various clinical illnesses (32-36). Furthermore, recent studies have shown that oxidative stress is related to cardiovascular diseases, such as coronary artery disease, acute myocardial infarction, metabolic syndrome, hypertension, and diabetes mellitus (5-10). This finding might be linked to endothelial dysfunction.

Ischemia-modified albumin (IMA) is a sensitive biomarker of ischemia and oxidative stress. Acidosis, reduced oxygen tension, and the generation of free radicals alter the binding capacity of albumin for cobalt. Some studies demonstrated that many clinical conditions may cause increased IMA levels, such as pulmonary embolism, mesenteric ischemia, and stroke (37-39). Finally, Türedi et al. (40) showed that IMA may be a valuable prognostic marker in CA patients following CPR. Similarly, in our present study, we showed that IMA levels increased in CA patients and were an independent predictor of failed CPR.

Reduction or termination of blood flow to the organs through to CA causes ischemic metabolic alterations. Restoration of blood circulation again, owing to CPR, oxygen, and leukocytes in the ischemic tissue, enhances the levels of chemokines, cytokines, complement, and adhesion molecules. These molecules amplify leukocyte activation; thus, leukocytes generate reactive oxygen species that cause damage to cellular proteins, the cytoskeleton, DNA, and mitochondria. These events result in life-threatening tissue damage. Consequently, it is supposed that both ischemia and reperfusion injuries are linked to death. Our study suggests that increased oxidative stress via ischemia-reperfusion injury, induced by CA and CPR itself, could potentially contribute to early mortality in CA patients.

Study limitations

Our study was limited by its monocentric nature, and hence, the findings should not be generalized to the overall population of patients with CA. The current study was also limited by its design, such that the study did not consider mid- to long-term outcomes after CPR, because the predictive role of the biomarker of interest is associated with very short outcomes. Of note, this study was only focused on immediate outcomes after CPR and hence gives no information about the outcomes after.

Lack of information with regard to previous chronic medications is also considered a limitation.

Conclusion

Admission OSI levels were detected to be increased in patients with CA. The OSI levels were observed to be higher in patients with failed CPR relative to successful CPR. In the presence of other clinical and laboratory parameters, admission OSI levels were shown to be an independent predictor of post-CPR early mortality. Eventually, an understanding and antagonism of oxidative stress in tissues could potentially improve survival in CA patients.

Conflict of interest: None declared.

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