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Original Article

Endoplasmic reticulum stress markers are of no value in predicting cardiopulmonary resuscitation success and survival in out-of hospital cardiac arrest: A nested case-control study

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ABSTRACT

Objectives: The purpose of this study was to determine the value of the endoplasmic reticulum (ER) stress markers glucose-regulated protein 78 (GRP78), C/EBP homologous protein (CHOP) and PERK in predicting the success of cardiopulmonary resuscitation (CPR) or post-CPR survival.
Materials and Methods: Non-traumatic out-of-hospital CA patients were included in this prospective, nested case-control study. Standard CPR and post-resuscitative care were applied. Levels of ER stress markers were measured at presentation and were investigated to determine whether they might constitute a marker predicting return of spontaneous circulation (ROSC) or sustained ROSC, and of 24-h, and 1 and 3-month survival.
Results: Fifty-two out of 99 non-traumatic CA patients were enrolled. ROSC was determined at a level of 25%, sustained ROSC at 23%, 24-h survival at 7%, and 1- and 3-month survival at 4.6%. No difference was determined in terms of ER stress markers between patients with and without ROSC or sustained ROSC. Only PERK levels were higher in surviving patients than non-surviving subjects in terms of 24-h survival ($p = 0.01$). Otherwise, no stress markers differed between surviving and non-surviving patients at any survival time point.
Conclusion: ER stress markers are of no value in determining establishment of ROSC or sustained ROSC, success of CPR, or survival. Only PERK levels may be valuable in terms of 24-h survival.

1. Introduction

1.1. Background

Cardiac arrest (CA), and particularly out-of-hospital cardiac arrest (OHCA), is a major public health problem with high mortality and morbidity rates.[1,2] Despite improvements in resuscitation techniques, survival and discharge rates for OHCA patients are lower than 16.2%.[3] Although various markers and tools have been investigated in terms of prognosis, return of spontaneous circulation (ROSC) and short-term survival are still difficult to predict.[1]

1.2. Importance

Practical and accurate parameters capable of assisting the clinician in such a critical procedure as cardiopulmonary resuscitation (CPR) and in determining the success of CPR and subsequent prognosis are still needed. Although the possible use of biochemical markers for that purpose was first mentioned in the 2015 guideline, these have been described as inadequate, and further research is still required.[2]

The endoplasmic reticulum (ER) is an organelle containing chaperone proteins and enzymes responsible for protein folding. The accumulation of unfolded or misfolded proteins in the ER is a cellular response resulting from impairment of ER homeostasis, known as ER stress.[3] Conditions such as ischemia, hypoxia, neurodegenerative diseases and diabetes lead to protein accumulation and associated toxic

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effects in the cell.[3,4] ER stress has been shown in ischemic, cardiac and neurological diseases, neurodegenerative diseases, sepsis, various cancers, inflammatory bowel diseases involving intestinal damage, and in renal diseases.[5–11] Glucose-regulated protein 78 (GRP78), C/EBP homologous protein (CHOP) and PERK are contemporary, novel biomarkers reflecting ER stress. Studies have concluded that GRP78, CHOP and PERK levels may be useful in diagnosis and prognosis in diseases involving increased ER stress.[5–11]

No previous studies have investigated ER stress in CA or the prognostic value of markers of ER stress. This study was planned around the hypothesis that ER stress is a dominant factor in CA patients and that ER stress markers may be valuable in predicting the success of CPR and subsequent prognosis.

1.3. Aim

The purpose of this study was to examine changes in levels of the ER stress markers PERK, CHOP and GRP78 in patients with OHCA and to determine whether these are of any prognostic value in terms of CPR success and post-CPR survival.

2. Materials and methods

2.1. Study design and setting

This prospective, single-center clinical study was carried out between November 2016 and November 2017, following receipt of ethical approval, at the Health Sciences University Trabzon Kanuni Training and Research Hospital Emergency Medicine Department, Turkey. The center where the study was performed is a tertiary emergency department serving a population of approximately 3 million and receiving 200,000 adult patients a year.

2.2. Selection of participants

Patients aged over 18 brought to the emergency department due to non-traumatic CA, whose rhythms were determined as pulseless electrical activity, asystole, ventricular fibrillation and pulseless ventricular tachycardia, irrespective of whether CPR had been started before arrival at hospital, were included in the study.

Patients with a history of cancer before CPR, patients transferred to our hospital from the intensive care units of other hospitals, traumatic CA cases, and in-hospital CA patients were excluded.

2.3. Study protocol

2.3.1. Data collection and processing

CA was defined as the cessation of spontaneous breathing efforts and the absence of any palpable pulses. All patients were resuscitated with chest compressions and defibrillation in line with the American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) protocol. Resuscitated subjects were managed in the intensive care unit with mechanical ventilation and appropriate therapies.[12]

In addition to demographic characteristics, clinical findings including type of arrest, site of arrest, whether pre-hospital CPR was performed, estimated cause of arrest, total duration of CPR, and arrest rhythms determined at start of and during CPR were recorded for all patients.

Blood specimens were collected in order to measure ER stress markers at the start of CPR. All patients were monitored throughout CPR, and success of resuscitation was determined in terms of ROSC and sustained ROSC. Post-resuscitation care of patients in whom ROSC was achieved after CPR was provided in line with the AHA 2015 guideline, which is still applied in relevant centers. The authors monitored mortality and potential additional problems throughout hospitalization until time of discharge. Neurological status at discharge of suitable patients was assessed using the Glasgow coma score (GCS) and Glasgow outcome score (GOS).

2.3.2. Definitions

CA was defined as the cessation of spontaneous breathing efforts and the absence of any palpable pulses. ROSC is defined based on a clinical assessment indicating signs of life comprising a palpable pulse or generation of blood pressure.[13] Sustained ROSC or a survived event is deemed to have occurred when chest compressions are not required for 20 consecutive minutes and signs of circulation persist.[13]

2.4. Laboratory measurements

2.4.1. Collection, storage and study of blood specimens

Ten-cubic centimeter venous blood specimens were collected from the peripheral veins at the start of CPR. These were centrifuged at 5000 rpm for 10 min in biochemistry tubes. The sera obtained were then stored at −80 0C in Eppendorf tubes.

PERK measurement: PERK levels in human serum were measured using an Enzyme-Linked Immunosorbent Assay kit (Abbkine, Cat No: KTE62752-2, Lot: ATRFE0501, China) in accordance with the manufacturer's instructions.

CHOP measurement: CHOP levels in human serum were measured using an Enzyme-Linked Immunosorbent Assay kit (Sunlong Biotech, Cat No: SL2631Hu, Lot: 201708, China) in accordance with the manufacturer's instructions.

GRP78 measurement: GRP78 levels in human serum were measured using an Enzyme-Linked Immunosorbent Assay kit (Sunlong Biotech, Cat No: SL2048Hu, Lot: 201708, China) in accordance with the manufacturer's instructions.

2.4.2. Follow-up

Discharged patients were evaluated in terms of mortality by telephone after one and three months. Surviving patients were invited to the hospital for check-ups, and their neurological status was evaluated using GCS and GOS.

2.4.3. Outcome measures

The primary outcome points of the study were the establishment of ROSC and sustained ROSC after CPR, while secondary outcome points were one- and three-month survival post-CPR.

2.4.4. Primary data analysis

Statistical analysis was performed on Statistical Package for Social Sciences for Windows v.23.0 (SPSS Inc., Chicago, IL, US) and MedCalc software v.11.5.1 (Medcalc software, Mariakerke, Belgium). Categorical data were expressed as count and frequency and numerical data as median and 25–75% percentiles. The Shapiro Wilk test was used to determine whether data were normally distributed at two-way comparisons, and comparisons between groups were performed using the Mann Whitney *U* test. An alpha value of 0.05 was regarded as the nominal level of significance.

Our study of ER stress and its markers in the success of CPR and prognosis in CA patients is a pioneering work in the field. From that perspective, and considering previous papers on the same subject, we targeted 50 OHCA patients.

3. Results

Forty-seven of the 99 patients with OHCA presenting to the center where the research was performed during the study period were excluded for various reasons. The study was therefore completed with 52 cases of OHCA (Table 1). A flow chart for the study is given in Fig. 1.

Table 1
Subjects' demographic and clinical characteristics.

Age mean ± SD		72 (± 16)
Sex n, %	Male	38 (73%)
	Female	14 (27%)
Arrest type n, %	Witnessed	46 (88.5%)
	Unwitnessed	6 (11.5%)
Arrest location n, %	Home	47 (90%)
	Garden	1 (2%)
	Airport	1 (2%)
	Street	2 (4%)
	Other	1 (2%)
Pre-hospital CPR n, %	No	42 (80%)
	Yes	10 (20%)
Cause of arrest n, %	Cardiac	44 (84.6%)
	Non-cardiac	8 (15.4%)
Arrest rhythm n, %	Asystole	44 (84.6%)
	NEA	4 (7.7%)
	VF	3 (5.8%)
	Pulseless VT	1 (1.9%)

3.1. CPR success

Figures of 25% ROSC and 23% sustained ROSC were achieved at the end of the study. PERK, CHOP and GRP78 levels of patients with and without ROSC and sustained ROSC are shown in Table 2. Analysis of the results revealed no difference between patients with and without ROSC and sustained ROSC in terms of CHOP, PERK or GRP78 levels.

3.2. Post CPR survival

Twenty-four hour survival was determined at 7%, with one- and three-month survival rates of 4.6%. PERK, CHOP and GRP78 levels in the surviving and non-surviving patients in terms of 24-h, and one- and three-month survival are shown in Table 3. Analysis showed that of the ER stress markers investigated, only PERK levels were higher in surviving patients than in non-surviving subjects in terms of 24-h survival ($p = 0.01$). Otherwise, no difference was determined among ER stress markers in surviving and non-surviving patients at any time interval.

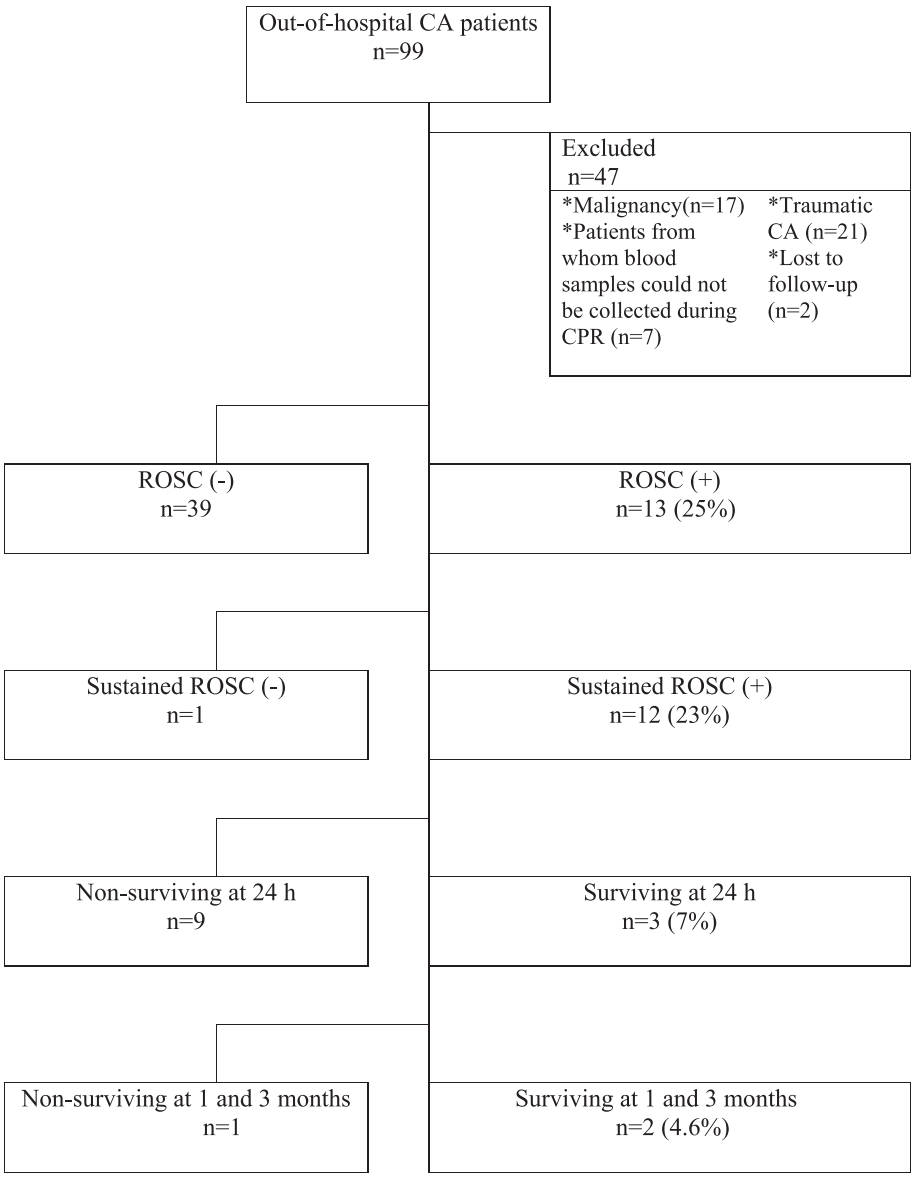

Fig. 1. Flow chart of the study.

Table 2
Comparison of PERK, CHOP and GRP78 levels in patients with and without ROSC and sustained ROSC in terms of success of CPR in OHCA patients.

		PERK Median (25–75%)	GRP 78 Median (25–75%)	CHOP Median (25–75%)
ROSC	Established	19.1 (18.6–24.8)	0.46 (0.27–1.31)	324.2 (86–690)
	Not established	18.9 (18.7–19.9)	0.46 (0.27–0.85)	225.9 (71–508)
	p value	0.453	0.975	0.492
Sustained ROSC	Established	18.9 (18–25)	0.47 (0.3–1.35)	311.8 (77–713)
	Not established	18.9 (18–20)	0.45 (0.26–0.84)	228.4 (75–505)
	p value	0.664	0.728	0.663

Table 3
Comparison of PERK, CHOP and GRP78 levels in surviving and non-surviving patients in terms of 24-h, and one- and three-month survival in OHCA patients.

		PERK Median (25–75%)	GRP 78 Median (25–75%)	CHOP Median (25–75%)
24 h survival	Non-surviving	18.9 (18.6–19.9)	0.46 (0.26–0.84)	240.4 (71–500)
	Surviving	25.9 (23–25)	1.23 (0.37–1.22)	643.4 (103–643)
	p value	**0.01**	0.231	0.231
1- and 3-month survival	Non-surviving	18.9 (18.6–20)	0.46 (0.27–0.85)	245.1 (71–509)
	Surviving	24.8 (23–24)	1.21 (0.37–1.20)	798.7 (103–798)
	p value	0.057	0.446	0.505

4. Discussion

Our study investigated the value of levels of the ER stress markers CHOP, PERK and GRP78 in predicting the success of CPR and prognosis in cases of OHCA. Establishment of ROSC and sustained ROSC as markers of successful CPR and survival at 24 h, and at one and three months, post-CPR were evaluated. To the best of our knowledge, ours is the first, precursor study of the role of ER stress in the success of CPR and survival and of whether or not ER stress markers can be used to predict these.

Our study results show that ER stress markers investigated at the beginning of CPR are of no value in predicting those patients with OHCA in whom ROSC and sustained ROSC will be achieved. Similarly, CHOP and GRP78 levels investigated at the start of CPR make no significant contribution to predicting survival in the first 24, or at one and three months. Only PERK was identified as potentially capable of predicting survival at 24 h post-CPR. Taking all these findings into account, markers of ER stress, which plays a significant role in the pathophysiology of the ischemic and hypoxic process in CA, investigated at the start of CPR appear to be of limited usefulness in terms of determining the success of CPR or survival.

ER is an organelle responsible for the folding, transportation, and maturation of membrane and secreted proteins. Another important function is to detect cellular stress. The principal functions of ER include determining whether protein folding is correct, rectifying misfolding, and breaking down misfolded proteins that cannot be rectified.[14] In the event of physiological and pathological conditions that exceed the functional capacity of ER, proteins are folded or misfolded in the ER lumen. This results in protein accumulation, known as ER stress. Under such conditions, unfolded or misfolded proteins compromise cellular homeostasis. Following the development of ER stress, a series of events consisting of various intracellular pathways known as the Unfolded Protein Response (UPR) are initiated to restore homeostasis in the cell and to enable it to recover from the stress with as little damage as possible. Cells primarily seek to ensure their survival by means of the UPR.[15–17] If the UPR is unable to resolve the problem inside the cell, the cell may have to apply one of two cell death mechanisms (apoptosis or autophagy).

UPR activation is brought about by ATF6 and IRE1, which act as ER stress sensors, and by PERK, one of the proteins measured in the present study.[17] Various events are then initiated, ranging from a decrease in protein synthesis to cell death. The principal situations capable of impairing ER homeostasis are biological conditions including infection, exposure to chemical toxins, lipid overaccumulation, deficient nutrition, and various genetic disorders, but particularly hypoxia.[9] These conditions may lead to an increase in ER stress and in PERK associated with such stress.

No clinical studies have investigated levels of the ER stress marker PERK in CA patients. However, two experimental studies both performed by Montie et al. investigated the relation between CA and PERK. In the first, the authors induced CA in rats and investigated ER stress at the tissue level in animals in which reperfusion and ROSC were established with CPR, assessing this by measuring PERK levels. They concluded that ER stress developed with CPR in CA, and that such stress was present at different levels in different tissues, thus causing variation between tissues in terms of responses to ER stress.[18] In the other study, Montie et al. established 10-min heart failure in rats by inducing CA, and then established ischemia-reperfusion with CPR. They reported an increase in ER stress and in PERK activation, a UPR marker.[19] In both studies, the authors evaluated PERK levels at the tissue level. Ours is an original clinical study assessing ER stress and PERK in the systemic circulation. The results of our research, which differ from earlier precursor studies, show that PERK levels measured in systemic blood cannot be used as a marker of whether or not ROSC or sustained ROSC have been established with CPR following CA. They are also not indicative of one- or three-month prognosis. They may, however, make a minor contribution to determining 24-h survival alone.

Under physiological conditions, aggregation of the PERK-mediated signal pathway is obstructed by the chaperone GRP78. Under conditions of ER stress, GRP78 is sent to the lumen to assist with folding when unfolded proteins accumulate. PERK aggregation is thus facilitated, and the UPR begins.[17] In other words, in the same way that PERK increases with ER stress, an increase in GRP78 levels may occur for the purpose of responding to or resisting stress in the early period. If this protective mechanism is ineffective, then cell death by apoptosis or autophagy ensues.

Although no clinical studies involving GRP78 have been performed with CA patients, GRP78 functions have been investigated in several different studies, and it has been shown to be potentially cardioprotective and neuroprotective. In one such study, Gupta et al. demonstrated that overexpression of GRP78 protects against ER stress in the cardiomyocytes. In addition, the Bag5 protein family was observed to regulate GRP78 expression.[20] Goldenberg-Cohen et al. investigated the role of cell surface GRP78 peptide binding to astrocytes and neurons in limiting cell death. They reported that the binding of ADoPep1 peptide to GRP78 on the cell surface protected astrocytes and neurons to a significant extent in both early and late apoptosis. The authors concluded that cell surface GRP78 on astrocytes and neurons can be used as

a target for neuroprotection.[21] Hardy et al. reported a significant increase in cell surface GRP78 in rats following exposure to severe stress conditions, such as 4-h hypoxia and fasting. Reducing the expression of GRP78 in cardiomyocytes under these hypoxic conditions was reported to have no effect on apoptosis. Additionally, reducing the expression of GRP78 in cardiomyocytes under milder stress conditions resulted in a higher survival rate compared with the production of GRP78 under the effect of UPR. Moreover, ADoPep1, a cell surface GRP78 binding peptide, was observed to protect the cardiomyocytes against hypoxia-related apoptosis.[22] In the light of all these findings, it appears that in CA, in which the ischemic and hypoxic process plays the most important role and in which the most severe neuronal damage occurs, GRP78 levels may rise as a response or resistance to these events, and that this elevation may be valuable in terms of the success of CPR and subsequent survival. However, on the basis of our own findings, GRP78 levels measured at the start of CPR are not capable of predicting ROSC or sustained ROSC or of determining survival.

Despite the response to increased GRP78 and ER stress, excessive and prolonged ER stress leads to the triggering of apoptotic processes regulated by transcriptional induction of CHOP (23). CHOP functions as a transcription factor, and despite being described as a response to DNA damage, its levels also rise under conditions of ER stress. Overexpression of CHOP has been shown to be proapoptotic. In other words, if the endeavor to resist ER stress by means of increases in PERK and GRP78 levels is insufficient (in case of severe or prolonged ER stress), CHOP expression rises in order to regulate apoptosis, and apoptosis then occurs.[17]

4.1. Limitations

Our study of ER stress and its markers in the success of CPR and prognosis in CA patients represents precursor research. From that perspective, and in the light of previous papers on the same subject, we targeted 50 OHCA patients, and the study was finally performed with 52. The number of patients involved in the study was relatively small. However, in terms of the novel hypothesis that ER stress markers constitute new diagnostic and prognostic biomarkers, our study may be regarded as pioneering and can serve as the basis for further, more comprehensive studies. Nonetheless, the low number of cases in our study means that the results are limited in terms of generalization and wide applicability.

As envisaged under the study design, only patients with OHCA were enrolled. No deductions are therefore possible concerning whether or not our results also apply to in-hospital CA patients.

Out-of-hospital traumatic CA cases and CA patients with known malignancy were excluded from this study. This resulted in a significant loss of cases, and our results cannot be generalized to this patient group. Since survival is very low in out-of-hospital arrest in cancer patients, health workers have to take difficult decisions, such as not to resuscitate or to keep resuscitation short. Cancer patients were excluded from our patients out of concern that this decision might affect one of our study's most important outcome points, and that our research might influence the resuscitation decision in these patients (such as the prolongation of a CPR procedure that might be kept shorter).

ER stress markers in our study were measured only at the start of CPR. No information was therefore obtained concerning changes in ER stress markers in patients surviving after CPR. ER stress in our study was examined only by means of PERK, GRP78 and CHOP measurements, previously identified as ER stress markers.

Finally, no analysis or comparison was performed concerning other biomarkers described as potentially capable of prognostic use after CPR in contemporary guidelines.

5. Conclusion

In conclusion, ER stress markers investigated at the start of CPR are of no value in predicting ROSC or sustained ROSC, success of CPR, or survival. Only PERK levels may be of some value in terms of 24-h survival.

Presented at a meeting

No

Grant

No

Conflicts of interests statement

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Author contributions

SA, SY, ST, SD, AM: substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published; GA, MI, SD: acquisition of data, interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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