American Journal of Emergency Medicine 34 (2016) 1561–1566

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Assessment of oxidative stress after out-of-hospital cardiac arrest

Jean-Christophe Orban, MD, PhD [a,*], Catherine Garrel, MD, PhD [b], Didier Déroche, MD [a], Florian Cattet, MD [a], Patricia Ferrari, MD [c], Frédéric Berthier, MD [d], Carole Ichai, MD, PhD [a]

[a] Intensive Care Unit, Pasteur Hospital, Nice University Hospital, Nice, France
[b] Pathology and Biology Institute, Grenoble University Hospital, Grenoble, France
[c] Biochemistry and Hormonology Laboratory, Pasteur Hospital, Nice University Hospital, Nice, France
[d] Department of Medical Information, Cimiez Hospital, Nice University Hospital, France

ARTICLE INFO

Article history:
Received 26 April 2016
Received in revised form 18 May 2016
Accepted 18 May 2016

ABSTRACT

Introduction: Pathophysiology of cardiac arrest corresponds to a whole body ischemia-reperfusion. This phenomenon is usually associated with an oxidative stress in various settings, but few data are available on cardiac arrest in human. The aim of the present study was to evaluate different oxidative stress markers in out-of-hospital cardiac arrest (OHCA) patients treated with therapeutic hypothermia.
Materials and methods: We conducted a prospective study assessing oxidative stress markers (thiobarbituric acid reactive species, carbonyls, thiols, glutathione, and glutathione peroxidase) in OHCA patients treated with therapeutic hypothermia. Measurements were performed during the 4 days after admission and compared between good and poor outcome patients according to Cerebral Performance Category.
Results: Thirty-four patients were included, 10 good and 24 poor outcomes at 6 months. Thiobarbituric acid reactive species were higher in the poor outcome group on admission and when therapeutic hypothermia was reached. The other markers were not different between groups. No markers seemed modified by the use of therapeutic hypothermia in each group.
Conclusions: After OHCA, good outcome patients exhibit lower oxidative stress markers than poor outcome patients. Thiobarbituric acid reactive species appears to be an early prognostic parameter. Oxidative stress markers seem not mitigated by therapeutic hypothermia.

© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a major health problem with a poor prognosis [1,2]. After resuscitation, unfavorable outcome results mainly from the complications of postreperfusion syndrome [3]. Refractory shock state and multiorgan failure are responsible of early fatalities. Lately, most of patients die of irreversible brain damage. Pathophysiology of resuscitated cardiac arrest represents a whole body ischemia/reperfusion. This phenomenon leads to an oxidative stress and a generalized nonspecific inflammation [4]. Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses levels. A massive generation of ROS occurs in the minutes after reperfusion, but few clinical studies confirmed these laboratory data [5]. Actually, ROS are very unstable with a short half-life, and their measurement techniques are cumbersome. Most of the time, oxidative stress markers are measured as a substitute of ROS because they are more stable. They reflect the interaction and the subsequent injuries of ROS with different cell components. Thiobarbituric acid reactive species (TBARS) and malondialdehyde (MDA) are specific of lipid peroxidation, and carbonyls reflect protein oxidation. On the other hand, reductions in antioxidant levels be it enzymatic (superoxide dismutase, catalase, glutathione peroxidase) or nonenzymatic (glutathione, thiols, vitamins…) are most frequently measured as indicators of oxidative stress. Thus, glutathione, one of the main antioxidants, is decreased in multiorgan failure patients [6]. The antioxidant enzyme glutathione peroxidase shows an increased activity when facing an oxidative stress situation. Several laboratory data begin to unravel the association between cardiac arrest and oxidative stress. For example, plasma lipid peroxidation and DNA damage marker are correlated to myocardial dysfunction in a model of cardiac arrest [7]. In another animal model, the level of oxidative stress due to the percentage of oxygen during reperfusion is associated to outcome [8]. Unfortunately, clinical data exploring the relations between oxidative stress and cardiac arrest are scarce. Endothelial cells incubated with plasma from cardiac arrest patients exhibit the features of oxidative stress with an increased ROS generation and a diminution of antioxidant defenses [9]. In another study, thioredoxin, a protein induced by oxidative stress and inflammation, was higher in nonsurvivor than in survivor after cardiac arrest [10].

* Corresponding author at: Réanimation Polyvalente et Surveillance Continue, Hôpital Pasteur, CHU de Nice, 30, voie Romaine, 06006 Nice Cedex, France. Tel.: +33 4 92 03 33 00.
E-mail address: orban.jc@chu-nice.fr (J.-C. Orban).

http://dx.doi.org/10.1016/j.ajem.2016.05.054
0735-6757/© 2016 Elsevier Inc. All rights reserved.

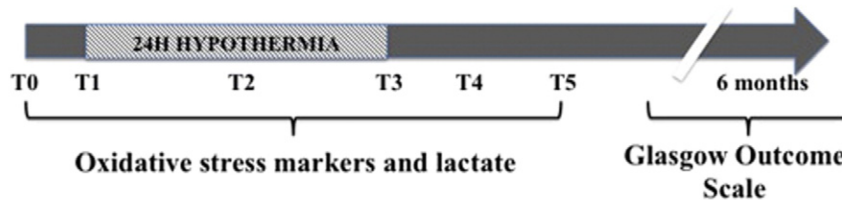

Fig. 1. Study protocol.

Therapeutic hypothermia has been used decades ago in the management of cardiac arrest patients, but its utilization waned due to complications [11]. Recent articles brought back this therapy under the light. To date, it is the only intervention improving mortality and neurologic outcome [12,13]. Several hypotheses were suggested to explain these effects: mitigation of the postreperfusion oxidative stress and inflammation, a decreased cerebral oxygen consumption, and reduction of excitotoxicity. Laboratory data support some of these assumptions, showing a decrease in oxidative stress correlated to therapeutic hypothermia [14,15]. However, few clinical data are available. Recently, it has been shown that temperature changes during therapeutic hypothermia and rewarming could affect the course of proinflammatory and anti-inflammatory molecules [16].

Because laboratory and clinical data suggest a temperature mitigation of oxidative stress, we investigated the changes in oxidative stress markers during therapeutic hypothermia after OHCA and their association with prognosis.

2. Materials and methods

2.1. Patient selection

After approval from the local ethics committee (Comité de Protection des Personnes Sud Méditerrranée V, study number 06.008), we included prospectively comatose patients resuscitated from an OHCA treated with therapeutic hypothermia. Written informed consent was obtained from the next of kin before enrollment. As therapeutic hypothermia is a standard of care, we considered unethical the comparison to a normothermic group. All patients aged 18 to 80 years admitted for OHCA from cardiac or respiratory causes were eligible. Those with resuscitation longer than 60 minutes, fraction of inspired oxygen higher than 60% 1 hour after admission, refractory shock, and moribund patients were excluded.

2.2. Patients' management

Once the prehospital team obtained return of spontaneous circulation, coronary angiography and percutaneous coronary intervention were performed if needed. Then patients were admitted to the intensive care unit of our tertiary care university hospital. According to ILCOR recommendations, patients were cooled to 34°C [17]. To reach this goal, external methods were used consisting of ice packs placed on main vascular accesses and torso and fans. Therapeutic hypothermia was maintained during 24 hours, followed by passive rewarming to normothermia (37°C). Temperature was continuously monitored by a Foley catheter with a temperature sensor (Level 1; Smith Medical ASD, Rockland, MA). Patients were given an association of midazolam and fentanyl during hypothermia and paralyzed using continuous infusion of cisatracurium. All patients were intubated and mechanically ventilated aiming at a Pa_{O_2} between 75 and 100 mm Hg and Pa_{CO_2} between 35 and 45 mm Hg. A central venous catheter was inserted in the subclavian or jugular vein, and an arterial line was inserted in the radial or femoral artery for monitoring of blood pressure and sampling of arterial blood. Mean arterial blood pressure was maintained greater than 80 mm Hg, and diuresis was aimed greater than 0.5 mL/kg per hour. Patients were given fluid infusion or dobutamine or norepinephrine to reach this goal, according to hemodynamic monitoring data. Hemoglobin concentration was kept greater than 10 g/dL. Glucose was maintained between 0.8 and 1.2 g/dL by continuous insulin infusion according to our local protocol.

Table
Demographic data of the population

	Study population	Good outcome (CPC 1 and 2)	Poor outcome (CPC 3-5)
Age (y)	58 (22-77)	60 (46-71)	57 (22-77)
No flow time (min)	10 (5-15)	13 (8-15)	10 (5-15)
Low flow time (min)	15 (10-30)	10 (5-30)	16 (10-30)

2.3. Study protocol

Assessment of oxidative stress was evaluated by different parameters: markers of lipid peroxidation (TBARS) and protein oxidation (carbonyls) and antioxidant defenses (glutathione, thiol radicals, glutathione peroxidase activity) (Fig. 1). These measurements were performed on arterial blood at different time points: on admission (T0), at 34°C (T1), after 12 hours at 34°C (T2), after 24 hours at 34°C (T3), after rewarming to 37°C (T4), and on day 4 (T5).

Arterial blood samples were collected in lithium heparin vacutainers as an anticoagulant. Four hundred microliters of whole blood was collected in 3.6 mL of metaphosphoric acid for the determination of total glutathione. After centrifugation (4000*g*, 10 minutes, 4°C), total glutathione was determined enzymatically in the acidic protein-free supernatant. The rest of whole blood was centrifuged to separate the plasma for thiols, TBARS, glutathione peroxidase, and carbonyls measurements. Plasma was collected in Eppendorff sterile tubes and stored at −80°C until assayed. Lipid peroxidation intermediates were measured by the plasma thiobarbituric acid reactive substances. Thiobarbituric acid reactive species are products of the oxidative degradation of polyunsaturated fatty acids, in particular MDA. We used the modified method of Ohkawa et al [18], based on the reaction of aldehyde functions of MDA released by acid hydrolysis at 95°C with thiobarbituric acid forming a pink-colored complex quantified by fluorimetry. Plasma carbonyl assay is based on the reaction of carbonyl groups in protein with 2,4-dinitrophenylhydrazine to form 2,4-dinitrophenylhydrazone, which was estimated spectrophotometrically at 380 nm after trichloroacetic acid precipitation of proteins. Glutathione peroxidase activity was determined by the modified method of Gunzler using *tert*-butyl hydroperoxide as substrate [19]. The measurement of plasma thiol groups was performed using Ellman's reagent and determined spectrophotometrically at 412 nm [20]. All reagents were purchased from Sigma (St Louis, MO).

Collected variables included the patient's demographic and prehospital data on admission ("no flow" and "low flow" durations, drugs infused, defibrillation). Hemodynamic parameters, temperature, and SpO_2 were measured continuously. Outcome was assessed using the Cerebral Performance Category scale (CPC) ranging from 1 to 5 at 6 months. Cerebral Performance Category 1 and 2 were considered favorable outcome, and CPC 3 to 5 were considered unfavorable.

Download English Version:

https://daneshyari.com/en/article/6078642

Download Persian Version:

https://daneshyari.com/article/6078642

Daneshyari.com