American Journal of Emergency Medicine 35 (2017) 846–854

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

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

Original Contribution

Correlation of Impedance Threshold Device use during cardiopulmonary resuscitation with post-cardiac arrest Acute Kidney Injury

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ARTICLE INFO

Article history:
Received 11 December 2016
Received in revised form 16 January 2017
Accepted 21 January 2017

Key words:
Cardiopulmonary resuscitation
Ventricular fibrillation
Impedance Threshold Device
Acute Kidney Injury
Neutrophil Gelatinase-Associated Lipocalin
Interleukin-18

ABSTRACT

Purpose: To assess whether use of Impedance Threshold Device (ITD) during cardiopulmonary resuscitation (CPR) reduces the degree of post-cardiac arrest Acute Kidney Injury (AKI), as a result of improved hemodynamics, in a porcine model of ventricular fibrillation (VF) cardiac arrest.

Methods: After 8 min of untreated cardiac arrest, the animals were resuscitated either with active compression-decompression (ACD) CPR plus a sham ITD (control group, $n = 8$) or with ACD-CPR plus an active ITD (ITD group, $n = 8$). Adrenaline was administered every 4 min and electrical defibrillation was attempted every 2 min until return of spontaneous circulation (ROSC) or asystole. After ROSC the animals were monitored for 6 h under general anesthesia and then returned to their cages for a 48 h observation, before euthanasia. Two novel biomarkers, Neutrophil Gelatinase-Associated Lipocalin (NGAL) in plasma and Interleukin-18 (IL-18) in urine, were measured at 2 h, 4 h, 6 h, 24 h and 48 h post-ROSC, in order to assess the degree of AKI.

Results: ROSC was observed in 7 (87.5%) animals treated with the sham valve and 8 (100%) animals treated with the active valve (P = NS). However, more than twice as many animals survived at 48 h in the ITD group ($n = 8$, 100%) compared to the control group ($n = 3$, 37.5%). Urine IL-18 and plasma NGAL levels were augmented post-ROSC in both groups, but they were significantly higher in the control group compared with the ITD group, at all measured time points.

Conclusion: Use of ITD during ACD-CPR improved hemodynamic parameters, increased 48 h survival and decreased the degree of post-cardiac arrest AKI in the resuscitated animals.

1. Introduction

Cardiac arrest (CA) constitutes a major medical problem with substantial socio-economic implications. It is estimated that every year about 350,000–700,000 people suffer CA in Europe, both in hospital and out of hospital [1,2], and the prognosis of the victims remains ominous despite the hard efforts of international organizations, such as the European Resuscitation Council (ERC) and the International Liaison Committee on Resuscitation (ILCOR), over the last three decades [3]. Even when cardiopulmonary resuscitation (CPR) is initially successful and the victim achieves Return of Spontaneous Circulation (ROSC), long term survival and quality of life are not guaranteed. Survival to hospital discharge ranges from 9.5% for out-of-hospital cardiac arrest (OHCA) victims to 24.2% for in-hospital cardiac arrest (IHCA) victims. Of the survivors, 40–50% remains with cognitive impairments, such as memory and intellectual performance deficits [4]. In severe cases, the patients present a persistent comatose state, becoming completely dependent; others minimally regain consciousness or remain in a vegetative state; and few come out of coma neurologically intact [5]. The

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http://dx.doi.org/10.1016/j.ajem.2017.01.040
0735-6757/

term "post-cardiac arrest syndrome" describes the myocardial, neurologic and other vital organs' (lungs, kidneys, liver) dysfunction, causing significant morbidity and mortality after ROSC. The mechanisms underlying this syndrome probably involve a whole-body ischemia and reperfusion injury that triggers a systemic inflammatory response [6-10].

These disappointing statistics can be attributed to several factors, such as the long time interval between the occurrence of CA and the initiation of CPR, the low quality CPR often performed by rescuers [11-13] and the inherent inability of classical CPR to supply vital organs with adequate blood flow during CA. During standard closed chest manual CPR the venous return from the periphery to the chest during decompression is inadequate. This is because a significant percentage of the negative intrathoracic pressure produced during decompression of the thorax is lost by the influx of inspiratory gases. Without adequate venous return to the heart, the pump will be empty during the subsequent compression phase and, therefore, blood supply to the vital organs will be minimized. To be more specific, standard CPR only provides 10–20% of normal blood flow to the heart and 20–30% of normal blood flow to the brain [14-16].

In order to enhance CPR efficiency numerous mechanical devices have been developed [17]. The Impedance Threshold Device (ITD) is a small valve with a silicon diaphragm that can be attached to an endotracheal tube, a supraglottic device or a face mask. It is designed to selectively impede inspiratory gas flow into the patient during the decompression phase, whereas it allows both active patient ventilation and passive exhalation. This way it enhances negative intrathoracic pressure and increases venous return to the heart and, therefore, cardiac output [18-22]. Numerous experimental and clinical studies have proved its value; ITD improves hemodynamics, perfusion of vital organs, ROSC, short-term survival, ICU admissions, survival to hospital discharge and long term survival with favorable neurologic function [14,20,23-51]. However, none of the above studies has investigated the effect of ITD use during CPR on the degree of post-CA Acute Ischemic Injury of other vital organs, except the myocardium and the brain. The aim of the present study is to assess whether use of ITD during CPR reduces the degree of post-CA Acute Kidney Injury (AKI) in a porcine model of VF cardiac arrest. Our hypothesis was that if ITD use improves hemodynamics during CPR, blood supply to the kidneys would be improved and, therefore, the degree of post-CA AKI would be lessened. In order to assess the degree of AKI two novel biomarkers were measured; Neutrophil Gelatinase-Associated Lipocalin (NGAL) in plasma and Interleukin-18 (IL-18) in urine.

2. Materials and methods

After approval of the General Directorate of Veterinary Services of Prefecture of Athens, Attica, Greece (permit no. 2980/9-5-2012), 16 female Landrace/Large-White piglets, aged 10–15 weeks, with an average weight of 19 ± 2 kg, all from the same breeder were studied. Before any procedure, animals were randomized into two groups with the use of sealed envelopes indicating the animals' assignment to either the active/functional ITD group (ITD group, $n = 8$) or the sham/nonfunctional ITD group (control group, $n = 8$). Sham ITDs were externally identical to the active ITDs, but internally were modified; the silicon diaphragms were removed so as the devices functioned as hollow conduits. This way, the investigators were blinded to the device function (active or sham).

2.1. Preparatory phase

The animals were prepared in a standardized fashion previously described [52], at ELPEN pharmaceuticals Experimental-Research Centre (Pikermi, Attica, Greece). Premedication was achieved by IM injection of ketamine hydrochloride (10 mg/kg), midazolam (0.5 mg/kg) and atropine (0.05 mg/kg). Anesthesia was induced with propofol (2 mg/kg) via the marginal auricular vein. Then, intubation was performed with a 4.0 or 4.5 mm cuffed endotracheal tube (Portex, ID Smiths Medical, Keene, NH). Subsequently, the animals were connected to a volume-controlled ventilator (Soxil, Soxitronic, Felino, Italy), with room air (FiO_2 21%) and a tidal volume of 15 ml/kg. End-tidal CO_2 ($ETCO_2$) was monitored with a side-stream infrared CO_2 analyzer and the respiratory frequency was adjusted to maintain $ETCO_2$ between 35 and 40 mm Hg. Cisatracurium (0.15 mg/kg) was administered to ascertain synchrony with the ventilator. Continuous infusion of propofol 150mcg/kg/min or more, if needed, was used to maintain anesthesia and fentanyl 4 mcg/kg was administered to ensure satisfactory analgesia. Cardiac rhythm and heart rate were monitored by electrocardiography (ECG), using leads I, II, III, aVR, aVL and aVF. Pulse oximetry was monitored continuously on the animals' tongue. Right carotid artery and right internal jugular vein were surgically prepared and cannulated under aseptic conditions. Aortic pressures were measured using a normal saline filled catheter (model 6523, USCI CR, Bart, Papapostolou, Athens, Greece) advanced via the right carotid artery into the thoracic aorta. Mean arterial pressure (MAP) was determined by electronic integration of the aortic blood pressure waveform. Right internal jugular vein was catheterized with a 6F sheath and a central vein catheter was inserted through the sheath into the right atrium for continuous measurement of right atrial pressures. All catheters were calibrated before use and their correct position was verified by the presence of the typical pressure waveforms. Coronary perfusion pressure (CPP) was calculated as the difference between decompression diastolic aortic pressure and time-coincident right atrial pressure, measured at the end of each minute of compressions.

2.2. Experimental protocol

Baseline data were obtained after a stabilization period of 30 min. VF was then induced with a 5F pacing wire (Pacel™, 100 cm, St Jude Medical, Ladakis, Athens, Greece) advanced into the right ventricle through the exposed right internal jugular vein, using a 9 V cadmium battery, as previously described [52]. VF was confirmed by ECG tracing and a sudden drop in MAP. Mechanical ventilation and administration of anaesthetics were discontinued simultaneously with the onset of VF and the animals were left untreated for 8 min (representing the average time of EMS arrival in OHCA in Europe [53]).

After 8 min of untreated cardiac arrest, CPR begun; a bolus dose of adrenaline (0.02 mg/kg) was administered, mechanical ventilation was resumed with 100% oxygen and automatic continuous precordial compressions were initiated. The sham or active ITD (ResQPOD, Advanced Circulatory Systems, Eden Prairie, MN) was placed directly on the proximal end of the ETT and the ventilator's breathing system was then directly connected to it. LUCAS CPR device (LUCAS, Jolife, Lund, Sweden) is a pneumatically driven, automated compression-decompression device, which provided high-quality chest compressions at a rate of 100/min and a compression depth equivalent to 1/3 of the anteroposterior diameter of the animals' thorax, with active recoil of the chest to the full resting position after each compression.

After 2 min of CPR, a 4 J/kg monophasic waveform shock was delivered. CPR was resumed for another 2 min after each defibrillation attempt. Further bolus doses of adrenaline (0.02 mg/kg) were administered every four minutes during CPR. This sequence was continued until ROSC or asystole. ROSC was defined as the presence of a perfusing cardiac rhythm with a MAP of at least 60 mm Hg for a minimum of 5 min.

After ROSC, the ITD was removed and the animals were mechanically ventilated and closely monitored for 6 h, under general anesthesia, at the pre-arrest settings. No other interventions (drugs, cardioversion or defibrillation attempts) were made after ROSC. After 6 h all catheters were removed. The animals were allowed to recover from anesthesia and, then, were extubated and transferred to their observation cages. They remained under observation for 48 h after ROSC and then