International Journal of Cardiology 186 (2015) 250–258

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Spectral analysis-based risk score enables early prediction of mortality and cerebral performance in patients undergoing therapeutic hypothermia for ventricular fibrillation and comatose status ☆

David Filgueiras-Rama [a,c,d,*,1,2], Conrado J. Calvo [b,e,2,3], Óscar Salvador-Montañés [d,3,4], Rosalía Cádenas [d,4], Jose Ruiz-Cantador [d,4], Eduardo Armada [d,4], Juan Ramón Rey [d,4], J.L. Merino [d,4], Rafael Peinado [d,4], Nicasio Pérez-Castellano [c,3], Julián Pérez-Villacastín [c,3], Jorge G. Quintanilla [a,3], Santiago Jiménez [b,3], Francisco Castells [b,e,3], Francisco J. Chorro [e,3], J.L. López-Sendón [d,3], Omer Berenfeld [f,3], José Jalife [a,f,3], Esteban López de Sá [d,3,4,5], José Millet [b,e,3,5]

[a] Atherothrombosis, Imaging and Epidemiology Department, Fundación Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain
[b] Bio-ITACA Grupo de Bioingeniería, Instituto de Aplicaciones Avanzadas, Dpto Ingeniería Electrónica, Universitat Politècnica de Valencia, Spain
[c] Hospital Clínico San Carlos, Madrid, Spain
[d] Hospital Universitario La Paz, IdiPaz, Madrid, Spain
[e] Grupo Electrofisiología y Bioingeniería, Microcluster en Protección Cardiovascular, Dpto de Medicina, Fundación INCLIVA Hospital Clínico, Valencia, Spain
[f] Center for Arrhythmia Research, Cardiovascular Research Center, Department of Internal Medicine, University of MI, Ann Arbor, USA

ARTICLE INFO

Article history:
Received 19 September 2014
Received in revised form 26 January 2015
Accepted 2 March 2015
Available online 14 March 2015

Keywords:
Cardiac arrest
Cerebral injury
Early prognosis
Ventricular fibrillation
Dominant frequency

ABSTRACT

Background: Early prognosis in comatose survivors after cardiac arrest due to ventricular fibrillation (VF) is unreliable, especially in patients undergoing mild hypothermia. We aimed at developing a reliable risk-score to enable early prediction of cerebral performance and survival.

Methods: Sixty-one out of 239 consecutive patients undergoing mild hypothermia after cardiac arrest, with eventual return of spontaneous circulation (ROSC), and comatose status on admission fulfilled the inclusion criteria. Background clinical variables, VF time and frequency domain fundamental variables were considered. The primary and secondary outcomes were a favorable neurological performance (FNP) during hospitalization and survival to hospital discharge, respectively. The predictive model was developed in a retrospective cohort ($n = 32$; September 2006–September 2011, 48.5 ± 10.5 months of follow-up) and further validated in a prospective cohort ($n = 29$; October 2011–July 2013, 5 ± 1.8 months of follow-up).

Results: FNP was present in 16 (50.0%) and 21 patients (72.4%) in the retrospective and prospective cohorts, respectively. Seventeen (53.1%) and 21 patients (72.4%), respectively, survived to hospital discharge. Both outcomes were significantly associated ($p < 0.001$). Retrospective multivariate analysis provided a prediction model (sensitivity = 0.94, specificity = 1) that included spectral dominant frequency, derived power density and peak ratios between high and low frequency bands, and the number of shocks delivered before ROSC. Validation on the prospective cohort showed sensitivity = 0.88 and specificity = 0.91. A model-derived risk-score properly predicted 93% of FNP. Testing the model on follow-up showed a c-statistic ≥ 0.89.

Conclusions: A spectral analysis-based model reliably correlates time-dependent VF spectral changes with acute cerebral injury in comatose survivors undergoing mild hypothermia after cardiac arrest.

Abbreviations: FNP, Favorable neurological performance; HL-PSDR, High-to-low power spectral density ratio; HL-pKR, High-to-low peak ratio.

☆ *Grant support*: the CNIC is supported by the Spanish Ministry of Economy and Competitiveness and the Pro-CNIC Foundation.

* Corresponding author at: Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernández Almagro 3, 28029 Madrid, Spain.
E-mail address: david.filgueiras@cnic.es (D. Filgueiras-Rama).

[1] This author designed and supervised the study, and takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Both authors contributed equally to this manuscript.
[3] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[4] This author contributed to data collection, review and interpretation.
[5] Both authors contributed as senior authors.

http://dx.doi.org/10.1016/j.ijcard.2015.03.074
0167-5273/

1. Introduction

Both in-hospital and out-of-hospital cardiac arrests due to ventricular fibrillation (VF) are associated with high mortality rates and significant cerebral disability [1,2]. VF-derived cerebral injury is a very sensitive time-dependent condition with dramatic social and personal consequences. The absence of cerebral blood flow during VF leads to ischemic damage within a few minutes, which increases after reperfusion due to generation of oxygen free radicals and activation of degradation enzymes, together with other mediators [3]. To date, mild hypothermia is the only therapy that has shown to increase both survival rates and functional outcomes in comatose survivors of cardiac arrest due to VF [4–6], even though cardiopulmonary resuscitation (CPR) technique and some specific drugs are considered influential to improve return of spontaneous circulation (RSOC) and survival outcomes during resuscitation [7–9]. However, the use of sedative and neuromuscular blocking drugs in cooled patients may mask neurological damage and delay examination. Furthermore, early prognosis within the first 72 h after cardiac arrest remains unreliable, which is especially relevant in those patients undergoing highly specialized intensive care who might not have any hopes for recovery.

Reducing the time to DC shock after VF onset is vital to restore spontaneous circulation and minimize cerebral injury [10]. However, the exact time in VF is difficult to determine even after witnessed cardiac arrest. Many VF episodes may initiate as ventricular tachycardia and cerebral blood flow might still persist until VF develops [11]. Reliable experimental data from waveform analysis during VF indicate that both spectral dominant frequency (DF) and median frequency decrease after onset of VF [12,13]. In the clinical setting, such a decrease in spectral values correlates with poor defibrillation success and no ROSC [14]. Moreover, retrospective data in patients with out-of-hospital cardiac arrest and VF have shown that a 5.61 Hz DF threshold can serve as a good predictor for 1-year survival after discharge [15]. Therefore, we hypothesize that spectral analysis of VF before a DC shock will accurately reflect the degree of acute cerebral injury as a consequence of time in VF and concomitant myocardial ischemia.

Here, we analyzed VF waveform properties before the first DC shock in patients undergoing therapeutic hypothermia due to comatose status after advanced life support (ALS) and ROSC. We aimed to identify spectral parameters that in combination with clinical variables may serve to develop a reliable model and risk score to enable early prediction of cerebral performance and survival to hospital discharge. We also studied the capacity of the model to predict both outcomes at follow-up.

2. Methods

2.1. Study design

The study was performed in a referral center for out-of-hospital cardiac arrest (Hospital Universitario La Paz, Madrid, Spain), in which mild therapeutic hypothermia is routinely used in comatose survivors after the event. The emergency service and ambulances in the region have trained medical staff and nurses, all coordinated by a central station to minimize both time to ALS and transportation to a referral center. The study included consecutive patients who underwent mild hypothermia after cardiac arrest due to VF, eventually with ROSC, and comatose status (Glasgow Coma Scale ≤ 8) on admission. Patients with witnessed or un-witnessed documented VF were eligible for the study, as long as VF traces before the first DC shock had enough quality and duration (≥ 3 s) for digitization and analysis of spectral parameters, respectively. We excluded patients with early mortality or hemodynamic instability leading to incomplete 24 h of mild hypothermia, and absence of subsequent withdrawal of sedation to assess cerebral performance. Other exclusion criteria were age <18 years, Glasgow Coma Scale score after ROSC >8, non-shockable or shockable rhythms other than VF, a terminal illness or cognitive deterioration present before the cardiac arrest, and possible causes of coma other than cardiac arrest. The study was divided into two groups, as follows: group 1 with eligible patients from September 2006 to September 2011 and retrospective data analysis, and group 2 with eligible patients from October 2011 to July 2013, in whom we prospectively studied the utility of the predictive algorithm developed in group 1. All data were collected from a prospective registry. The institutional ethics review committee approved prospective analysis of the patients, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and European guidelines for good clinical practice.

2.2. Hypothermia protocol

Patients admitted to the acute cardiac care unit (ACCU) underwent routine neurological evaluation before sedation, drug-induced paralysis and initiation of hypothermia protocol as described elsewhere [6]. Briefly, cooling with intravenous cold saline (<8 °C) was initiated on admission. This was followed by direct cooling of the blood using the Icy catheter (ZOLL Medical Corporation, Chelmsford, MA) positioned at the level of the inferior vena cava through the femoral vein. Cooling was set at a maximum rate with a target temperature either at 32, 33 or 34 °C, which was maintained during 24 h. Rewarming was controlled at a set rate of 0.1 to 0.3 °C/h to reach 37 °C in 12 to 24 h. Mechanical ventilation was adjusted to ensure normoxemia and normocapnia. Mean blood pressure was maintained between 85 and 100 mm Hg. Blood glucose level was ensured at <10 mmol/l. Limitation of active ALS was considered in patients who remained deeply comatose after 5 days of evolution, as long as it was possible to reach an agreement with their representatives.

2.3. Spectral analysis

For each patient, we analyzed VF epochs prior to the first DC shock. Digitization was performed using a supervised semi-automatic approach based on region of interest selection, histogram thresholding and intensity transformations. Up to 5-s long segments were extracted after segmentation and signal codification from artifact-free VF tracings. Signals were band-pass filtered between 1.5 and 40 Hz. Quality of extraction was visually inspected by two independent investigators. Averaged power spectral density was obtained at each frequency using the non-parametric Welch method for using fast Fourier transform and normalized to the peak power in the 1.5–10 Hz band for each patient. Both time and frequency domain variables were quantified across patients. Those included VF amplitude over time, amplitude spectral area (AMSA), DF, median frequency, approximate entropy regularity index, spectral regularity index, 1-Hz DF spectral concentration and normalized 80% power spectral density (see Fig. 1 and Supplemental Methods for details). Investigators blinded to clinical outcome performed all data analysis, extraction and quantification using custom-made scripts of MATLAB software (V. 2010b, The Mathworks, Inc., Natick, MA).

2.4. Outcome

The primary outcome was a favorable neurological performance (FNP) during hospitalization. All patients were classified using the Pittsburgh outcome categorization of brain injury as follows: cerebral performance categories (CPCs) 1 and 2 (good and moderate disability, respectively) were considered as FNP, and CPCs 3, 4 and 5 (severe disability, vegetative state and brain death, respectively) were considered as a non-FNP (Supplemental Table 1) [16]. Neurological outcome was established after in-hospital stabilization or before hospital discharge. In patients from group 1, retrospective data were obtained from clinical records during hospitalization.

The secondary outcome measure was survival to hospital discharge.