Resuscitation 99 (2016) 20–25

Contents lists available at ScienceDirect

Resuscitation

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

Experimental paper

Whole body periodic acceleration (pGz) preserves heart rate variability after cardiac arrest☆

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ARTICLE INFO

Article history:
Received 24 September 2015
Received in revised form 3 November 2015
Accepted 16 November 2015

Keywords:
Cardiac arrest
Resuscitation
Heart rate variability
Whole body periodic acceleration
Nitric oxide
Neuronal nitric oxide

ABSTRACT

Aims: Heart rate variability (HRV) is a measure of the balance between the sympathetic and parasympathetic autonomic nervous system and lack thereof an ominous sign in many cardiac and neurological conditions including post-cardiac arrest syndrome. Whole body periodic acceleration (pGz) has been shown to be cardio protective when applied prior to during and after cardiac arrest (CA). Here, we investigate whether or not pGz pre or post treatment after CA preserves HRV.

Methods: Eight min of unsupported ventricular fibrillation followed by CPR and defibrillation was carried out in 32 anesthetized and paralyzed male swine who were randomized to pretreatment (1 h pGz prior to CA, pre-pGz [$n = 8$]) or post-treatment (pGz beginning at 30 min after return of spontaneous circulation ([ROSC], post-pGz [$n = 8$]) or none (CONT [$n = 8$]). pGz was applied together with conventional mechanical ventilation. In a separate group ($n = 8$), infusion of TRIM (nNOS inhibitor) was used to determine the effects of nNOS inhibition on HRV.

Results: Time and frequency domain measures of HRV were determined along with measurements of blood gases and hemodynamics, obtained at baseline and at 30, 60, 120 and 180 min after ROSC. All animals had ROSC and there were no significant differences for arterial blood gases, mean blood pressure and coronary perfusion pressure after ROSC among the groups. HRV was significantly depressed after cardiac arrest and remained depressed in CONT group. In contrast, both pre and post pGz treated groups had significantly higher and preserved time domain measures of HRV (RMSSD and SDNN) from 60 to 180 min after ROSC, and nNOS inhibition markedly reduced HRV. The frequency domain of HRV did not show changes.

Conclusions: In a pig model of CA, pre or post treatment with pGz preserves HRV. Inhibition of nNOS markedly reduced HRV. Post-treatment with pGz is a novel therapeutic strategy that might serve as an adjunct to current pharmacological or hypothermia modalities to potentially improve outcomes from post-cardiac arrest syndrome.

Introduction

Heart rate variability (HRV) represents the variation between successive cardiac beats as measured from electrocardiographic R–R intervals and reflects autonomic nervous system (ANS) balance and function. Post-cardiac arrest loss of HRV has been associated with increased mortality and poor neurological outcome.[1–5]

Cardiac arrest (CA) and resuscitation is a model of whole body ischemia reperfusion injury. Post-resuscitation injury from cardiac arrest produces myocardial stunning, global cerebral injury and microcirculatory dysfunction along with uncoupling of the ANS and cardiovascular system.[6–9] Interventions (mechanical or pharmacological) to improve outcomes from cardiac arrest are desperately needed. We have previously shown that pGz employed as a pre-treatment (pre-pGz) or post-treatment (post-pGz) strategy in various models of cardiac arrest (VF and Asphyxia) in pigs decreases post resuscitation myocardial stunning, improves microcirculatory flows to vital organs and decreases markers of myocardial injury post arrest.[10–12] In this study we investigated the effects of pre or post pGz on post-cardiac arrest HRV in a pig model of VF induced cardiac arrest.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2015.11.018.

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http://dx.doi.org/10.1016/j.resuscitation.2015.11.018
0300-9572/

Materials and methods

Animal preparation

This study has been reported as to comply with the Utstein-Style Guidelines for Uniform Reporting of Laboratory CPR Research. This protocol was approved by the Institutional Animal Care and Use Committee of Mount Sinai Medical Center and conforms to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996) Protocol No. 13-09-A-03. Thirty two male pigs weighing 20 ± 5 kg were used in this study. The animals initially received a single dose of ketamine (10 mg/kg, i.m.) and were then maintained in a surgical plane of anesthesia with intravenous propofol. Propofol was discontinued upon cardiac arrest and no further anesthetics were used during the return of spontaneous circulation period. An airway was established by direct laryngoscopy and intubation. All animals were paralyzed with pancuronium bromide (0.1 mg/kg) to avoid gasping during cardiac arrest. Ventilation was controlled with a mechanical ventilator (Puritan Bennett, Pleasanton, CA) set at 10 ml/kg tidal volume and fractional inspired oxygen concentration (FiO_2) of 0.21% with frequency varied to achieve an arterial carbon dioxide tension between 35 and 45 mmHg. Intravascular catheters were placed in the femoral artery, left external jugular vein to the right atrium. The following measurements were obtained: mean blood pressure (BPm), mean right atrial pressure (RAPm), core body temperature. Mean coronary perfusion pressure (CPPm) was calculated from the difference between mid-diastolic BP and mid-diastolic RAP. Arterial blood gases measured using a blood gas analyzer (Rapid Lab TM348, Bayer Diagnostics, Tarrytown, NY).

Body temperature was maintained between 36 °C and 38 °C by means of a heating pad. Hemodynamic and blood gas measurements were analyzed at; baseline (BL1), baseline 2 after 1 h pre-treatment with pGz (BL2), and at 30, 60, 120, 180 min (ROSC 30, ROSC 60, ROSC 120, ROSC 180) after ROSC. Three sets of electrodes were placed on the animal's chest. A bipolar fibrillating electrode was placed subcutaneously across the apex of the heart to deliver 30 V of AC current at 60 Hz to induce VF. A standard three-lead electrocardiogram (ECG) Lead II configuration was used for continuous monitoring. A pair of defibrillating electrodes (Fast Patch® Plus, Medtronic Emergency Response Systems, Redmond, WA) connected to a LifePak Defibrillator (Medtronic Emergency Response Systems, Redmond, WA) was placed across the anterior-posterior chest to defibrillate the heart.

Platform design

The motion platform that imparts pGz has been previously described.[13,14] The link below depicts a schematic and video of the platform and motion: http://www.floridaheart.org/the-pgz-motion-platform/

Experimental design

Prior to surgery and catheter placement, animals were randomized to receive pre-pGz for 1 h prior to cardiac arrest, post-pGz beginning 30 min after return of circulation and continuing until end of protocol or control (CONT). Respiration was controlled with a mechanical ventilator throughout the entire study for all groups. VF was electrically induced and no interventions were instituted for eight min. All groups then received closed chest compression/ventilation cardiopulmonary resuscitation (CPR) using a pneumatic piston device (Thumper™, Michigan Instrument, Grand Rapids, MI) at a compression ventilation ratio of 30:2. The compression force was adjusted to decrease the anterior-posterior diameter of the chest by 25–30% using a maximal pressure of 70 lb/in^2. Defibrillation was then initiated by a series of monophasic electroshocks of 3–6 J/kg until return of spontaneous circulation (ROSC) up to a maximum of 15 electroshocks. FiO_2 (0.21) was maintained during CPR and after ROSC. No drugs were administered during CPR or after ROSC. Animals randomized to the pre-pGz group, received pGz for 1 h immediately prior to cardiac arrest, those randomized to the post-pGz group, pGz was started thirty min after return of circulation (to simulate the time period from out of hospital cardiac arrest to arrival at a hospital) and continued until 180 min after ROSC. pGz was carried out at a frequency of 180 cycles/min and acceleration in the z-plane (Gz) of ± 3.9 m/s^2 together with conventional mechanical ventilatory support. pGz was stopped for 15 min for artifact free ECG recording. Another group of animals was placed on the pGz platform without activation to serve as controls (CONT). All animals were continuously monitored for 3 h after ROSC and then humanely euthanized with 100 mg/kg of sodium pentobarbital while still under anesthesia, a method consistent with the recommendation of the Panel on Euthanasia of the American Veterinary Medical Association. Investigators analyzing the echocardiographic and hemodynamic data and HRV measurements were blinded to treatment assignment.

Neuronal nitric oxide inhibition

Since pGz increases protein expression of nNOS in the heart[15,16] which has a positive role in excitation contraction coupling,[17] eight additional animals received an intravenous bolus of 1 mg/kg of 1-(2-trifluoromethylphenyl)imidazole (TRIM, a nNOS selective inhibitor) followed by a 50 μg/kg/min intravenous infusion for 2 h. The effects of nNOS inhibition on HRV analysis were determined.

Heart rate variability analysis

The methods used for HRV analysis adhere to the standards developed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[18] RR intervals were obtained from the digitized electrocardiographic signals at a sample rate of 500 Hz. The consecutive RR intervals, which were the time intervals between successive pairs of QRS complexes where detected by using R wave detection. (LabChart7 Pro, ADInstruments, Colorado Springs, CO).

HRV was assessed by time and frequency domain methods from three 5-min consecutive RR intervals at baseline (BL1), baseline 2 (after pre-treatment with pGz, BL2), and at 30, 60, 120, 180 min (ROSC 30, ROSC 60, ROSC 120, ROSC 180) after ROSC. All ectopic beats resulting from premature ventricular contraction were removed from electrocardiographic waveforms and missing data replaced by interpolated beats derived from the nearest valid data, for analysis of normal R–R intervals, NN. The variables used for the time domain analysis include: mean RR intervals (RRM), standard deviation of all normal RR intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD). Frequency domain measures were determined using a standard Fast Fourier spectral analysis and the following calculated on the NN time intervals; very low frequency power (VLF, 0.01–0.04 Hz), low-frequency power (LF, 0.04–0.15 Hz), and high-frequency power (HF, 0.15–0.4 Hz). VLFP, LF, and HF powers are reported in normalized units (VLFPnu, LFnu, and HFnu), which represent the relative value of each power component in proportion to the total power.[19]

Statistical analyses

All values are reported as means ± SD. Continuous variables were evaluated by analysis of variance for repeated measures. For