ELSEVIER

Resuscitation 66 (2005) 71–81

RESUSCITATION

www.elsevier.com/locate/resuscitation

Pyruvate improves cardiac electromechanical and metabolic recovery from cardiopulmonary arrest and resuscitation☆

Arti B. Sharma, E. Marty Knott, Jian Bi, Rodolfo R. Martinez, Jie Sun, Robert T. Mallet *

Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, TX 76107-2699, USA

Received 4 August 2004; received in revised form 5 December 2004; accepted 5 December 2004

Abstract

Severe depletion of myocardial energy and antioxidant resources during cardiac arrest culminates in electromechanical dysfunction following recovery of spontaneous circulation (ROSC). A metabolic fuel and natural antioxidant, pyruvate augments myocardial energy and antioxidant redox states in parallel with its enhancement of contractile performance of stunned and oxidant-challenged hearts. This study tested whether pyruvate improves post-arrest cardiac function and metabolism. Beagles were subjected to 5 min cardiac arrest and 5 min open-chest cardiac compression (OCCC: 80 compressions min^{-1}; aortic pressure 60–70 mmHg), then epicardial dc countershocks (5–10 J) were applied to restore sinus rhythm. Pyruvate was infused i.v. throughout OCCC and the first 25 min ROSC to a steady-state arterial concentration of 3.6 ± 0.2 mM. Control experiments received NaCl infusions. Phosphocreatine phosphorylation potential (∼PCr) and glutathione/glutathione disulfide ratio (GSH/GSSG), measured in snap-frozen left ventricle, indexed energy and antioxidant redox states, respectively. In control experiments, left ventricular pressure development, d*P*/d*t* and carotid flow initially recovered upon defibrillation, but then fell 40–50% by 3 h ROSC. ST segment displacement in lead II ECG persisted throughout ROSC. ∼PCr collapsed and GSH/GSSG fell 61% during arrest. Both variables recovered partially during OCCC and completely during ROSC. Pyruvate temporarily increased ∼PCr and GSH/GSSG during OCCC and the first 25 min ROSC and enhanced pressure development, d*P*/d*t* and carotid flow at 15–25 min ROSC. Contractile function stabilized and ECG normalized at 2–3 h ROSC, despite post-infusion pyruvate clearance and waning of its metabolic benefits. In conclusion, intravenous pyruvate therapy increases energy reserves and antioxidant defenses of resuscitated myocardium. These temporary metabolic improvements support post-arrest recovery of cardiac electromechanical performance.

Keywords: Cardiac arrest; Electrocardiography; Free radical; Metabolism; Open-chest cardiac compression (OCCC); Stunning; Myocardial

1. Introduction

Despite recent progress in delivery of emergency medical care, cardiac arrest remains the leading cause of death in the United States and Western Europe. Only a minority of victims survive to hospital discharge [1], even when arrest occurs in the hospital [2]. Cardiopulmonary resuscitation (CPR) remains the only available intervention to sustain the victim until cardioversion; however, the systemic arterial pressures generated by CPR are inadequate to prevent ischemic deterioration of underperfused organs, including the heart. Cardiac injury during arrest and resuscitation culminates in post-arrest cardiac insufficiency, the 'post-resuscitation syndrome' [3] characterized by low cardiac output, hemodynamic instability and myocardial stunning [3,4].

Ischemic tissue injury is caused by ATP depletion, which compromises energy dependent processes that maintain cellular function and integrity and reactive oxygen species (ROS) that attack and disable cellular proteins. Even brief periods of cardiac arrest threaten energy reserves and com-

☆ A Spanish and Portuguese translated version of the Abstract and Keywords of this article appears at 10.1016/j.resuscitation.2004.12.016.

Abbreviations: AOP, mean aortic pressure; ARR, cardiac arrest; BL, pre-arrest baseline; CPR, cardiopulmonary resuscitation; Cr, creatine; dP/dt_{max}, dP/dt_{min}, maximum and minimum rates of left ventricular pressure change; GSH, glutathione; GSSG, glutathione disulfide; LVEDP, left ventricular end-diastolic pressure; OCCC, open-chest cardiac compression; PCr, phosphocreatine; ∼PCr, phosphocreatine phosphorylation potential (i.e. [PCr]/{[Cr][Pi]}); P_i, intracellular inorganic phosphate; ROSC, recovery of spontaneous circulation

* Corresponding author. Tel.: +1 817 735 2260; fax: +1 817 735 5084.
E-mail address: malletr@hsc.unt.edu (R.T. Mallet).

0300-9572/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2004.12.016

promise function and viability of cardiomyocytes. Although interventions that preserve cellular energy resources and minimize ROS formation could interrupt the pathogenesis of cardiac injury during CPR, such interventions remain elusive.

Pyruvate, a natural aliphatic monocarboxylate and product of glycolysis, has been found to be protective against ischemic and oxidant-induced injury of the myocardium [5–8]. A readily oxidized metabolic fuel, pyruvate bolsters cytosolic energy state, thereby providing energy to maintain cellular processes, including Ca^{2+} transport [9,10] in the face of metabolic challenges. Pyruvate also functions as an antioxidant [11,12]. Recent studies in this laboratory demonstrated that pyruvate increased glutathione (GSH) and NADPH redox potentials in stunned [13] and H_2O_2-challenged [14] guinea-pig hearts. Pyruvate also has proven effective in in situ hearts of large mammals. For example, pyruvate restored contractile function of stunned canine [15] and porcine [8] myocardium and decreased infarction following prolonged coronary occlusions in pigs [16].

This study tested the ability of pyruvate to improve post-arrest mechanical function, preserve energy resources and bolster antioxidant defenses in in situ canine hearts. Pyruvate was infused systemically throughout open-chest cardiac compression (OCCC) and the first 25 min of post-defibrillation recovery. Pyruvate treatment increased myocardial energy state during OCCC and glutathione redox state following defibrillation. Moreover, pyruvate hastened electrocardiographic recovery, increased left ventricular contractility during the early recovery period and lessened later declines in cephalic blood flow. These results suggest that pyruvate, by providing crucial metabolic energy and antioxidant support, could protect the myocardium during CPR, and thus, facilitate post-arrest cardiac recovery.

2. Materials and methods

2.1. Surgical preparation, instrumentation and electrocardiography

Animal experimentation was approved by the Animal Care and Use Committee of the University of North Texas Health Science Center and conformed to the *Guide for the Care and Use of Laboratory Animals* (NIH Publication 85–23, revised 1996). Adult beagles (8–16 kg; 33 males, 31 females) were fasted overnight, then randomly assigned to the pyruvate, NaCl vehicle or sham control groups described below. Dogs were sedated with morphine sulfate (3 mg kg^{-1} s.c.) and anesthetized with α-chloralose (100 mg kg^{-1} i.v.; Sigma, St. Louis, MO). Supplemental α-chloralose was administered as needed to maintain anesthesia. The dogs were intubated and mechanically ventilated (Harvard Apparatus Respirator) with room air enriched with supplemental oxygen. Vinyl cannulae were inserted into the femoral arteries and advanced into the abdominal aorta for measurement of blood pressure and blood sampling. Arterial pH, PO_2 and PCO_2 were kept within their respective physiological limits (7.35–7.45, 95–105 and 35–45 mmHg) by administering $NaHCO_3$ i.v. and by adjusting tidal volume and ventilatory frequency. Femoral veins were cannulated for administration of sodium pyruvate or NaCl and supplemental anesthetic. Core temperature was monitored with a rectal thermometer and maintained at 36–37 °C with heating pads. A Transonic 2SB flow probe was placed around the left common carotid artery for measurement of cephalic blood flow.

Standard limb lead II electrocardiogram was continuously monitored. ST segment displacement, an early measure of cardiac ischemic injury [17,18], was determined from the vertical deflection of the ST segment relative to the TP segment. ST displacement was expressed as a fraction of the vertical QRS deflection to control for between-experiment differences in signal amplitude.

The heart was exposed via a left lateral thoracotomy through the fifth intercostal space and suspended in a pericardial cradle. A Millar Instruments model SPR-5243F pressure transducer was inserted into the left atrial appendage and advanced into the left ventricle to monitor intraventricular pressure, the rate of pressure change (dP/dt) and heart rate. A vinyl cannula was placed in the right atrium and its distal end connected to a Statham pressure transducer to monitor right atrial pressure and to administer intracardiac medications during the arrest/resuscitation protocol. Positive end-expiratory pressure of 2 cm H_2O was applied following thoracotomy to prevent atelectasis. Hemodynamic and electrocardiographic data were acquired with IOX-Base-8 and IOX-Cardio-8 software (EMKA Technologies, Falls Church, VA).

2.2. Cardiac arrest and cardiopulmonary resuscitation protocol

Baseline measurements were taken after post-surgical stabilization. Ventricular fibrillation arrest was initiated by applying 9 V current to the left ventricular epicardium. Mechanical ventilation was interrupted at the onset of cardiac arrest. At 4.5 min arrest, a 1 mg bolus of epinephrine (adrenaline) was injected into the right atrium. Internal CPR was continuously administered between 5 and 10 min arrest by OCCC (80 compressions min^{-1}) to establish and maintain a mean aortic pressure of approximately 60 mmHg. The dogs were mechanically ventilated at 12 cycles min^{-1} during CPR. At 10 min arrest, a 5 J dc countershock was delivered to the epicardium with internal paddles (Burdick dc-190 defibrillator). In the event that the first countershock failed to achieve cardioversion, intervening OCCC was performed during the 30 s interval before the next attempt. Up to four 5 J countershocks, followed by up to three 10 J countershocks were administered, with intervening OCCC. One dog could not be defibrillated and was excluded from further analysis. Recovery of spontaneous circulation (ROSC) was confirmed by spontaneous cardiac depolarization and mean aortic pressure ≥60 mmHg. $NaHCO_3$ (10 mEq) was injected into the right