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Original Contribution

2,3-Butanedione monoxime facilitates successful resuscitation in a dose-dependent fashion in a pig model of cardiac arrest☆

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ABSTRACT

Purpose: Ischemic contracture compromises the hemodynamic effectiveness of cardiopulmonary resuscitation (CPR) and resuscitability from cardiac arrest. In a pig model of cardiac arrest, 2,3-butanedione monoxime (BDM) attenuated ischemic contracture. We investigated the effects of different doses of BDM to determine whether increasing the dose of BDM could improve the hemodynamic effectiveness of CPR further, thus ultimately improving resuscitability.
Methods: After 16 minutes of untreated ventricular fibrillation and 8 minutes of basic life support, 36 pigs were divided randomly into 3 groups that received 50 mg/kg (low-dose group) of BDM, 100 mg/kg (high-dose group) of BDM, or an equivalent volume of saline (control group) during advanced cardiovascular life support.
Results: During advanced cardiovascular life support, the control group showed an increase in left ventricular (LV) wall thickness and a decrease in LV chamber area. In contrast, the BDM-treated groups showed a decrease in the LV wall thickness and an increase in the LV chamber area in a dose-dependent fashion. Mixed-model analyses of the LV wall thickness and LV chamber area revealed significant group effects and group-time interactions. Central venous oxygen saturation at 3 minutes after the drug administration was 21.6% (18.4-31.9), 39.2% (28.8-53.7), and 54.0% (47.5-69.4) in the control, low-dose, and high-dose groups, respectively ($P < .001$). Sustained restoration of spontaneous circulation was attained in 7 (58.3%), 10 (83.3%), and 12 animals (100%) in the control, low-dose, and high-dose groups, respectively ($P = .046$).
Conclusion: 2,3-Butanedione monoxime administered during CPR attenuated ischemic contracture and improved the resuscitability in a dose-dependent fashion.

1. Introduction

Ischemic contracture, which refers to a progressive left ventricular (LV) wall thickening following ischemia, occurs frequently in prolonged cardiac arrest [1,2]. In a study of 59 out-of-hospital cardiac arrest (OHCA) patients who underwent open-chest cardiopulmonary resuscitation (CPR), firm myocardium indicating contracted heart muscle was present in 36 patients (61%) immediately after thoracotomy [2]. Ischemic contracture results in progressive decreases in LV chamber volume and corresponding decreases in stroke volume during CPR, which, in turn, compromise resuscitability following arrest [1–3].

Previous studies in isolated hearts suggested that reperfusion with 2,3-butanedione monoxime (BDM) reduced ischemic contracture and improved myocardial functional recovery after ischemia [4,5]. We previously compared the effects of 50 mg/kg of BDM with placebo in a pig model of OHCA [6]. In this study, BDM administered during CPR attenuated ischemic contracture significantly, but the improvement of resuscitability by BDM over placebo did not reach statistical significance. Several studies suggest that BDM inhibits myocardial ischemic contracture in a dose-dependent manner [7,8]. Thus, it can be hypothesized that increasing the dose of BDM can improve the hemodynamic effectiveness of CPR further, thus ultimately improving resuscitability. However, to our knowledge, the dose-response effects of BDM have not been studied in an in vivo cardiac arrest model.

In this study, we investigated the effects of different doses of BDM in a pig model of OHCA to determine whether a higher dose of BDM could further attenuate ischemic contracture during CPR and improve resuscitability and short-term survival.

2. Methods

Thirty-six domestic pigs weighing 21.6 kg (19.7–22.9) were used. The Animal Care and Use Committee of Chonnam National University approved the protocol of this study (CNU IACUC-H-2015-19).

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Animal care and experiments were conducted according to the author's Institutional Animal Care and Use Committee guidelines.

2.1. Animal preparation

After premedication (ketamine, 20 mg/kg; xylazine, 2.2 mg/kg), anesthesia was induced with 50%:50% N_2O/O_2 and 2%-5% sevoflurane via a mask. After tracheal intubation, pigs were ventilated at a tidal volume of 15 mL/kg. Anesthesia was continued with 70%:30% N_2O/O_2 and 0.5%-2% sevoflurane titrated to prevent signs of pain. Ventilatory rates were adjusted to achieve normocapnia. A double-lumen catheter was advanced from the right femoral artery to the thoracic aorta to monitor aortic pressure and sample blood. The right external jugular vein was cannulated with an 8F introducer sheath to monitor right atrial (RA) pressure, to obtain a blood sample, and to insert a right ventricle (RV) pacing catheter. For echocardiographic measurements, a transesophageal echocardiography probe (UST-5293-5; Hitachi Aloka Medical Ltd, Tokyo, Japan) was inserted precordially into the mediastinum, as described previously [6]. We used this method to obtain an adequate LV long-axis view during CPR without interrupting chest compression. In our previous experience, in which the transesophageal echocardiography probe was advanced into the esophagus, chest compression frequently precluded adequate imaging of the LV. However, with this method, no interruption in chest compression or ventilation was required to visualize the LV during CPR. With regard to the doses of BDM, the dose used in the previous study (50 mg/kg) was chosen as the low dose [6] and 100 mg/kg, 2 times higher than the low dose, was chosen as the high dose. Immediately before inducing ventricular fibrillation (VF), an investigator opened a sealed envelope that assigned animals to 1 of 3 groups (control group, low-dose group, or high-dose group) and prepared either a saline placebo or BDM solution (Samchun Pure Chemical Co Ltd, Pyeongtaek, Korea; 25-g/L concentration solution for low-dose group, 50-g/L concentration solution for high-dose group) in equal volume (2 mL/kg). All other investigators involved in this study remained blinded to treatment allocation until analysis.

2.2. Experimental protocol

After baseline measurements, VF was induced by applying an electrical current (60 Hz, 30 mA alternating current) via the RV pacing catheter (Fig. 1). After 16 minutes of untreated VF, basic life support (BLS) using cycles of 30 chest compressions followed by 2 ventilations with ambient air was started. Closed-chest compressions were administered by 2 investigators (SSC and SML) blinded to the randomization in all animals at a rate of 100/min and a compression depth of 25% of the anterior-posterior diameter of the chest wall. After 8 minutes of BLS, advanced cardiovascular life support (ACLS) was initiated according to current resuscitation guidelines [9]. Positive-pressure ventilations with high-flow oxygen (10 L/min) were provided at a rate of 8/min. At the commencement of ACLS, all animals received 0.5 U/kg of vasopressin intravenously. At 2 minutes after the start of ACLS, either 50 mg/kg (low-dose group) or 100 mg/kg (high-dose group) of the BDM or an equivalent volume of 0.9% saline solution was administered into the RA. After 4 minutes of ACLS, 0.02 mg/kg of epinephrine was administered every 3 minutes if required. During ACLS, defibrillation was attempted using a single biphasic 150-J electric shock at 2-minute intervals. *Sustained restoration of spontaneous circulation* (ROSC) was defined as an unassisted pulsatile rhythm with a systolic aortic pressure greater than 60 mm Hg maintained for at least 10 minutes [10]. If ROSC was not achieved within 12 minutes of ACLS, resuscitation efforts were discontinued.

Animals that achieved ROSC received mechanical ventilation with 100% O_2 at prearrest settings and underwent a 4-hour period of intensive care. Five minutes after ROSC, oxygen concentration was reduced to 40%, and the ventilatory rate and/or tidal volumes were adjusted to achieve normocapnia. Recurrent cardiac arrest was treated with standard CPR according to current resuscitation guidelines [9]. Mean arterial pressure was maintained at >65 mm Hg with norepinephrine infusion. Throughout the intensive care period, titrated doses of sevoflurane were administered to maintain adequate anesthesia. At the end of the 4-hour period, animals were euthanized by infusing potassium chloride.

2.3. Measurements

Aortic pressure, RA pressure, and electrocardiogram were monitored (CS/3 CCM; Datex-Ohmeda, Helsinki, Finland) and transferred to a personal computer (S/5 Collect software; Datex-Ohmeda). Coronary perfusion pressure (CPP) was calculated by subtracting RA end-diastolic pressure from simultaneous aortic end-diastolic pressure. Arterial blood gases (RapidLab865; Bayer Health Care, Fernwald, Germany) and lactate (Unicel DXC 800; Beckman Coulter, Fullerton, CA) were measured at prearrest baseline, 5 minutes, and 4 hours after ROSC. At 5 minutes after the start of ACLS, a blood sample was obtained from the introducer sheath inserted into the RA to assess central venous oxygen saturation ($S_{cv}O_2$). Troponin-I (Dimension RXL Max; Siemens Healthcare Diagnostics, Deerfield, IL) was measured at prearrest baseline and at 4 hours after ROSC. Echocardiograms were obtained by a researcher blinded to the treatment allocation at the prearrest baseline (5 minutes before the induction of VF), during untreated VF (1, 8, and 16 minutes after the initiation of VF) and CPR (every 2 minutes during BLS and every minute during ACLS), and at 30 minutes and 4 hours after ROSC. An experienced, blinded observer analyzed the echocardiographic images. LV chamber area and LV wall thickness during CPR were measured using a technically satisfactory LV long-axis view of the frame

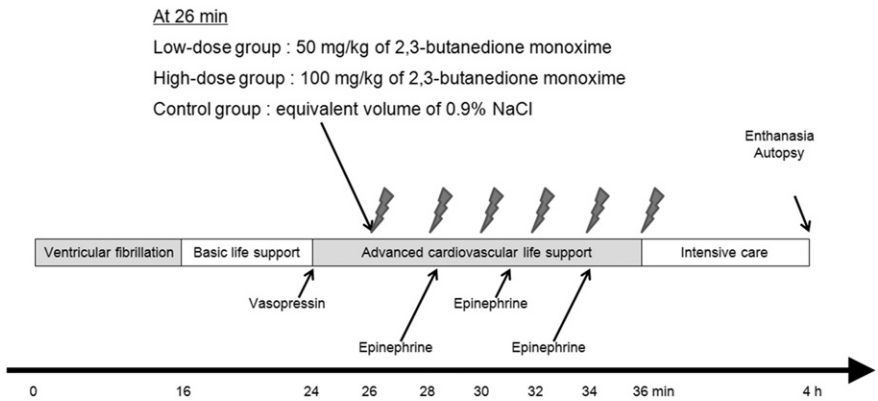

Fig. 1. Experimental timeline. At 2 minutes after the start of advanced cardiac life support (26 minutes after the VF induction), either 50 mg/kg (low-dose group) or 100 mg/kg (high-dose group) of the BDM or an equivalent volume of 0.9% saline solution was administered into the right atrium. The lightning marks indicate the onset of a 10-second pause in chest compressions for rhythm analysis and a 150-J shock if indicated.