Resuscitation 87 (2015) 26–32

Contents lists available at ScienceDirect

Resuscitation

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

Experimental paper

Effects of the administration of 2,3-butanedione monoxime during conventional cardiopulmonary resuscitation on ischaemic contracture and resuscitability in a pig model of out-of-hospital cardiac arrest☆,☆☆

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ARTICLE INFO

Article history:
Received 25 June 2014
Received in revised form 3 November 2014
Accepted 5 November 2014

Keywords:
Myocardium
Ischaemic contracture
Heart arrest
Cardiopulmonary resuscitation

ABSTRACT

Aim of the study: Ischaemic contracture compromises the haemodynamic effectiveness of cardiopulmonary resuscitation and resuscitability. 2,3-Butanedione monoxime (BDM) reduced ischaemic contracture by inhibiting actin-myosin crossbridge formation in an isolated heart model. We investigated the effects of BDM on ischaemic contracture and resuscitation outcomes in a pig model of out-of-hospital cardiac arrest (OHCA).

Methods: After 15 min of untreated ventricular fibrillation, followed by 8 min of basic life support, 16 pigs were randomised to receive either 2 ml kg^{-1} of BDM solution (25 g l^{-1}) or 2 ml kg^{-1} of saline during advanced cardiac life support (ACLS).

Results: During the ACLS, the control group showed an increase in left ventricular (LV) wall thickness from 10.0 mm (10.0–10.8) to 13.0 mm (13.0–13.0) and a decrease in LV chamber area from 8.13 cm^2 (7.59–9.29) to 7.47 cm^2 (5.84–8.43). In contrast, the BDM group showed a decrease in the LV wall thickness from 10 mm (9.0–10.8) to 8.5 mm (7.0–9.8) and an increase in the LV chamber area from 9.86 cm^2 (7.22–12.39) to 12.15 cm^2 (8.02–14.40). Mixed model analyses of the LV wall thickness and LV chamber area revealed significant group effects and group-time interactions. Spontaneous circulation was restored in four (50%) animals in the control group and in eight (100%) animals in the BDM group ($p = 0.077$). All the resuscitated animals survived during an intensive care period of 4 h.

Conclusion: BDM administered during cardiopulmonary resuscitation reversed ischaemic contracture in a pig model of OHCA.

1. Introduction

Ischaemic contracture, characterised by progressive left ventricular (LV) wall thickening with reductions in LV chamber volume, is a myocardial abnormality that occurs frequently in prolonged cardiac arrest.[1–3] It results from cross-bridge formation between actin and myosin following severe adenosine triphosphate depletion.[4,5] Several studies have indicated that ischaemic contracture compromises haemodynamic effectiveness of cardiopulmonary resuscitation (CPR) and, thus, resuscitability following cardiac arrest.[1,3,6]

2,3-Butanedione monoxime (BDM) has been shown to possess a negative inotropic effect by decreasing calcium sensitivity of contractile proteins, by attenuating intracellular calcium transient, or by inhibiting the force-producing cross-bridge formation between actin and myosin.[7–10] Several experimental studies in an isolated heart model indicated that BDM reduced ischaemic contracture as well as myocardial injury.[11–13] The reduction of ischaemic contracture may enhance the haemodynamic effectiveness of CPR by ensuring that larger LV volumes are maintained before each chest compression, thus facilitating successful resuscitation. However, to

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.11.011.
☆☆ Chonnam National University Hospital Animal Care Committee Protocol Number – CNU IACUC-H-2013-31.
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http://dx.doi.org/10.1016/j.resuscitation.2014.11.011
0300-9572/

our knowledge, no study has examined the effect of BDM in an in vivo cardiac arrest model.

In this study, we investigated the effects of BDM administered during CPR on ischaemic contracture and resuscitation outcomes using a pig model of out-of-hospital cardiac arrest (OHCA). We hypothesised that BDM would reduce ischaemic contracture and have favourable effects on resuscitability and short-term survival.

2. Methods

Sixteen male domestic pigs weighing 24.0 kg (22.6–25.7) were used. The Animal Care and Use Committee of Chonnam National University approved the protocol of this study. 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^{-1}; xylazine, 2.2 mg kg^{-1}; atropine, 0.04 mg kg^{-1}, intramuscular), anaesthesia was induced with 50%:50% N_2O:O_2 and 2–5% sevoflurane via a mask. After tracheal intubation, the pigs were ventilated at a tidal volume of 15 ml kg^{-1}. Anaesthesia 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 catheter was inserted into an ear vein and saline was administered to maintain a right atrial (RA) pressure of 6–12 mmHg. A double-lumen catheter was advanced from the right femoral artery to the thoracic aorta for monitoring aortic pressure and blood sampling. The right external jugular vein was cannulated with an 8-French introducer sheath to monitor RA pressure, and to insert a right ventricle (RV) pacing catheter. For echocardiographic measurements during CPR, a skin incision was made to the right of the xiphoid process. Then, a 4–5 cm pocket, wide enough to ensure free passage of a transoesophageal echocardiography (TEE) probe (UST-5293-5, Hitachi Aloka Medical Ltd., Tokyo, Japan), was made under the right side of the sternum.[14,15] The TEE probe was then inserted through the pocket. The manipulative controls of the TEE probe were used to obtain LV long-axis view allowing visualisation of the entire LV at the maximum obtainable chamber size while avoiding LV foreshortening. Electrocardiogram leads were placed on limbs to monitor heart rhythm. Rectal temperature was maintained between 37.5 °C and 38.5 °C. BDM (Samchun Pure Chemical Co Ltd., Pyeongtaek, Korea) was diluted in distilled water to obtain a concentration of 25 g l^{-1} for administration.

2.2. Experimental protocol

The experimental timeline is shown in Fig. 1. After baseline measurements, ventricular fibrillation (VF) was induced by passing 60 Hz of AC current at 30 mA through the RV pacing catheter for 4 s, and the animals were disconnected from ventilatory support. Immediately after inducing VF, an investigator, otherwise uninvolved with this study, opened a sealed envelope that assigned animals to either the control group or the BDM group. All other investigators involved in this study remained blinded to the treatment allocation until analysis. After 15 min of untreated VF, basic life support (BLS) was started, using cycles of 30 chest compressions followed by two ventilations with ambient air. Closed-chest compressions were administered by two investigators (SSC and SML) in all animals at a rate of 100 min^{-1} and a compression depth of 25% of the anterior-posterior diameter of the chest wall. This depth has been used as an optimal compression depth for pigs in several previous studies.[16,17] After 8 min of BLS, advanced cardiac life support (ACLS) based on current resuscitation guidelines was started.[18] At the start of ACLS, all animals received 0.5 U kg^{-1} of vasopressin intravenously. In our previous experiences, animals that received adrenaline (epinephrine) after prolonged untreated VF showed very low rates of restoration of spontaneous circulation (ROSC). In this study, we used vasopressin for both groups to increase the rate of ROSC, thus enabling evaluation of the effects of BDM on post-ROSC haemodynamic function. Previous studies on pigs suggest that, compared to adrenaline, vasopressin increases the rate of ROSC after prolonged cardiac arrest.[19] Asynchronous positive-pressure ventilations with high flow O_2 (10 l min^{-1}) were provided at a rate of 8 min^{-1} using a manual resuscitator bag. One minute after the start of ACLS, a 2 ml kg^{-1} bolus of BDM solution (BDM group) or a 2 ml kg^{-1} of 0.9% NaCl (control group) was administered into the RA. The administration of the BDM solution or the saline placebo was repeated 3 min after the start of ACLS. This dosing strategy was chosen based on our preliminary experiments on two pigs, which differed from the main experiments in that the animals underwent 15 min of untreated VF with subsequent low-flow extracorporeal membrane oxygenation (ECMO) support (10 ml kg^{-1} min^{-1}), the BDM solution was administered 3 min after the start of ECMO support, and no vasopressor was administered during resuscitation. In the preliminary experiments, the effects of BDM on LV wall thickness were fully established 1 min after the administration of the solution, and the effects disappeared within 3 min after the administration. After 2 min of ACLS, defibrillation was attempted with a single biphasic 150-J electric shock if indicated. If an organised cardiac rhythm with a mean aortic pressure of >60 mmHg persisted for an interval of ≥1 min, the animals were regarded as successfully resuscitated. If ROSC was not achieved, an additional 2 min of CPR was given before the next 10-s hands-off pause for rhythm analysis. If the cardiac rhythm was shockable, defibrillation was reattempted. After 4 min of ACLS, 0.02 mg kg^{-1} of adrenaline was administered every 3 min if required. This procedure was continued until ROSC was attained, or until 12 min had lapsed since the start of ACLS, when resuscitation efforts were discontinued.

Animals that achieved ROSC received mechanical ventilation with 100% O_2 at pre-arrest settings, and then underwent a 4-h period of intensive care. Five minutes after achieving ROSC, oxygen concentration was reduced to 40% and the ventilator settings were adjusted to achieve normocapnia. Mean arterial pressure was maintained at >65 mmHg with noradrenaline (norepinephrine) infusion. Throughout the intensive care period, titrated doses of sevoflurane were administered to maintain adequate anaesthesia. At the end of the 4-h period, animals were euthanised by infusing potassium chloride. Autopsy was routinely performed to document potential injuries to the thoracic and abdominal cavity during CPR.

2.3. Measurements

Aortic pressure, RA pressure, and standard lead II electrocardiogram were continuously monitored (CS/3 CCM, Datex-Ohmeda, Helsinki, Finland) and transferred to a personal computer by S/5 Collect software (Datex-Ohmeda, Helsinki, Finland). 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, USA) were measured at pre-arrest baseline and 5 min and 4 h after ROSC. Echocardiogram was obtained by a researcher blinded for the treatment allocation at pre-arrest baseline, during untreated VF and CPR, and at 30 min and 4 h after ROSC. A single experienced observer blinded to the experimental groups analysed the echocardiograhic images. LV chamber area and LV wall thickness during CPR were measured using a technically satisfactory LV long-axis view of the frame showing maximal dimension of the LV chamber following release of chest compression. The LV chamber