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The beneficial hemodynamic effects of afterload reduction by sodium nitroprusside during rewarming from experimental hypothermia

Brage Håheim [a], Timofey Kondratiev [a], Erik Sveberg Dietrichs [a, c], Torkjel Tveita [a, b, *]

[a] Anesthesia and Critical Care Research Group, Department of Clinical Medicine, UiT, The Arctic University of Norway, 9037 Tromsø, Norway
[b] Division of Surgical Medicine and Intensive Care, University Hospital of North Norway, 9038 Tromsø, Norway
[c] Department of Research and Education, Norwegian Air Ambulance Foundation, 1441 Drøbak, Norway

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ABSTRACT

Background: Rewarming from hypothermia is associated with depressed cardiac function, known as hypothermia-induced cardiac dysfunction (HCD), and increased systemic vascular resistance (SVR). Previous studies on pharmacological treatment of HCD have demonstrated beneficial effects when using drugs with the combined effects; cardiac inotropic support and peripheral vasodilation. The presented study aims to investigate the isolated effects of arterial dilatation on cardiac functional variables during rewarming from hypothermia using sodium nitroprusside (SNP).

Methods: We utilized a rat model designed to induce HCD following 4 h at 15 °C and rewarming. To study effects on left ventricular (LV) functional variables in response to afterload reduction by SNP during rewarming a conductance catheter was used. Index of LV contractility, preload recruitable stroke work (PRSW), was obtained with inferior vena cava occlusions at 37 °C before and after hypothermia. Pressure signals from a catheter in the left femoral artery was used to pharmacologically adjust SVR.

Results: After rewarming both animal groups showed significant reduction in both SV and CO as a manifestation of HCD. However, compared to saline controls, SV and CO in SNP-treated animals increased significantly during rewarming in response to afterload reduction displayed as reduced SVR, mean arterial- and end-systolic pressures. The cardiac contractility variable PRSW was equally reduced after rewarming in both groups.

Conclusion: When rewarming the present model of HCD a significant increase in SVR takes place. In this context, pharmacologic intervention aimed at reducing SVR show clear positive results on CO and SV. However, a reduction in SVR alone is not sufficient to fully alleviate CO during HCD, and indicate the need of additional inotropic support.

1. Background

Hypothermia-induced cardiac dysfunction (HCD) is a well-known and life-threatening complication that may occur during treatment of accidental hypothermia victims [5,28,38]. In experimental models of hypothermia and rewarming, HCD has been identified as a key mechanism underlying rewarming shock [35,39]. Being a feared complication, rewarming shock develops as the cardiovascular system fails to provide adequate perfusion during rewarming and contributes to the high lethality in accidental hypothermia victims [5,28], reported to be between 28 and 35% [22,31,42]. Clinically, patients present with symptoms of low cardiac output (CO) accompanied by a rapid drop in blood pressure, despite restoration of core temperature [5].

Previous experiments have reported positive effects of milrinone and levosimendan on stroke volume (SV) and CO and when applied during rewarming in attempts to alleviate HCD [6,7]. The documented increase in cardiac function of these drugs is mainly attributed their direct positive inotropic effects. However, the

Abbreviations: LV, Left ventricle; MAP, Mean arterial pressure; HR, Heart rate; ESP, LV end-systolic pressure; dP/dt max, Maximum rate of LV pressure change; dP/dt min, Minimum rate of LV pressure change; SV, Stroke volume; CO, Cardiac output; SVR, Systemic vascular resistance; SW, Stroke work; PRSW, Preload recruitable stroke work; SNP, Sodium Nitroprusside; HCD, Hypothermia-induced cardiac dysfunction; CPC, Cardiac pumping capacity.

* Corresponding author. Anesthesia and Critical Care Research Group, UiT, The Arctic University of Norway, 9037 Tromsø, Norway.
E-mail addresses: bha035@post.uit.no (B. Håheim), timofey.kondratiev@uit.no (T. Kondratiev), erik.sveberg.dietrichs@uit.no (E.S. Dietrichs), torkjel.tveita@uit.no (T. Tveita).

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beneficial effects were accompanied by a reduction in mean arterial pressure (MAP) and systemic vascular resistance (SVR) explained by the well documented vasodilating effects of these drugs [26]. In normal physiology, vasodilatation reduces SVR and alleviate cardiac work and afterload, elevating CO [11]. This has also been demonstrated in patients with ischemic heart failure and cardiogenic shock where SVR reduction improved left-ventricular function and CO [3]. The beneficial effects of levosimendan and milrinone on HCD stand in contrast to the effects of adrenaline documented in the same experimental model. Unlike levosimendan or milrinone, adrenaline increased SVR and failed to alleviate CO during hypothermia and rewarming [8,12,19].

Cardiovascular physiology research has demonstrated that the relationship between CO and MAP is determined by four principal factors; SVR, cardiac pumping capacity (CPC), blood volume, and vascular compliance [11]. The beneficial effects of levosimendan and milrinone to elevate CO take place by simultaneously increasing CPC by Ca^{2+}-sensitization and phosphodiesterase-3 inhibition and by reducing SVR via peripheral vasodilation through opening of smooth muscle K^{+}_{ATP}-channels and phosphodiesterase-3 inhibition [26]. As both SV and SVR are altered in HCD, the combined pharmacological effects of levosimendan and milrinone, to support cardiac inotropy and induce vasodilatation, complicate the interpretation of the hemodynamic data. In a quest to ameliorate and understand HCD and rewarming shock, it is important to determine the separated effects of vasodilatation and positive inotropy.

Different from milrinone and levosimendan, sodium nitroprusside (SNP) is a potent vascular vasodilator with no inotropic effects [33]. It has been meticulously studied and are readily used in both clinical practice and in basic research and has demonstrated to improve cardiac function during cardiogenic shock and when used *after* rewarming from hypothermia in dog [3,24,32,34]. SNP relax smooth muscle and reduce SVR by nitric oxide activation of the cGMP-pathway. In vitro studies report possible inotropic support of SNP on cardiomyocytes [18,23]. However, *in vivo* experiments finds no clinical relevant changes in contractile parameters in healthy and failing hearts [33].

The aim of this study is to investigate if reduction in SVR during rewarming from experimental hypothermia may improve cardiac function. To test this we applied SNP in comparison with non-treated saline controls in a well-established *in vivo* rat model of HCD equipped for invasive hemodynamic monitoring [6,7,19].

2. Materials and methods

2.1. Animals

Male Wistar rats (n = 14, mean weight 313.8 g ± 7.18) were used. Animals were obtained from Charles River and quarantined for 1 week before experiment. Housing was provided in accordance with guidelines for accommodation and care of animals (article 5 of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, Strasbourg, 18.III.1986). The rats had a microbiological status per the recommendation of the Federation of European Laboratory Animal Science Associations. The animals had ad libitum access to water and food. The experimental protocol was approved by the Norwegian Animal Research Authority and conducted accordingly.

2.2. Anesthesia

Before vivisection, the animals were anesthetized with 50 mg/kg sodium pentobarbital and 0.05 mg/kg fentanyl with an intraperitoneal bolus injection. The animals received 7.5 mg/kg/h sodium pentobarbital and 0.05 mg/kg/h fentanyl through a pediatric central venous catheter placed in the right jugular vein. Cold narcosis occurs <30 °C, pharmacological anesthesia was therefore discontinued <30 °C and continued upon rewarming [27]. Pain and discomfort was monitored with the toe-pinch method as well as hemodynamic markers of stress. Toe-pinch is a well-known and established method to determine the depth of anesthesia in rodents [4,7,19].

2.3. Respiratory support

Airways were secured by a tracheostomy followed by insertion of a tracheal tube. In this model apnea occurred at around 20 °C, whereby mechanical ventilation with a small rodent ventilator is started (Kent Scientific, USA). Mechanical ventilation was discontinued once spontaneous respiration returned upon rewarming.

2.4. Hemodynamic measurements

Continuous cardiac volume and pressure measurements were provided through cannulation of the left carotid artery with a 2.0 French conductance catheter (SPR-838, Millar Instruments Inc., USA) placed in the left ventricle [2]. The conductance catheter technique and calibration is previously described in detail in earlier reports [6,7,12]. A fluid filled 22G catheter placed in the left femoral artery provided systemic arterial pressure measurement. Both catheters were connected to a PowerLab 16/30 transducer (ADInstruments, New Zealand), and the data was recorded and analyzed using LabChart 7 (ADInstruments, New Zealand). Hemodynamic data was recorded at 37 °C, 32 °C, 28 °C, 24 °C, 20 °C, and hourly for 4 h at 15 °C. To assess cardiac contractility, preload recruitable stroke work (PRSW) was obtained by occluding the inferior vena cava at 37 °C baseline and after rewarming. The reduced hemodynamic function during hypothermia <20 °C prohibited vena cava occlusions and therefore PRSW values was not obtainable during the hypothermia protocol [6,10].

2.5. Cooling and rewarming

Temperature control was obtained with a water bath (Thermostat water bath type RTE-110, Neslab Instruments, USA) circulating cold or warm water through a U-shaped polyethylene tube gently inserted into the intestine. In addition, the water bath was connected to a hollow, double walled, aluminum surgical table providing external heating and cooling. Temperature was continuously monitored with the use of an esophageal thermocouple (T-type) connected to a transducer (Colombia Instruments, USA). Both cooling and rewarming of the animals lasted 90 min, while the hypothermic period lasted 4 h (Fig. 1).

2.6. Sodium nitroprusside and saline

Sodium nitroprusside (Nitropress®) from Hospira (IL, USA) (25 mg/mL) was used. On the day of experiment, the sodium nitroprusside stock was diluted to 0.125 mg/ml (1:200) in 5% glucose [17]. As placebo in the saline control group 0.9% NaCl (Fresenius Kabi, Germany) was used.

2.7. Experimental design and pharmacological intervention

Two experimental groups were included in this study. Group 1 – Saline and Group 2 – Nitroprusside. After surgery, all animals received 1 mL saline with 10 IE Heparin/mL and were allowed to stabilize for 1 h before cooling. Both groups were subjected to 4 h of hypothermia at 15 °C with subsequent rewarming. Pharmacological

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