Cryobiology 69 (2014) 361–366

Contents lists available at ScienceDirect

Cryobiology

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

Milrinone ameliorates cardiac mechanical dysfunction after hypothermia in an intact rat model ☆

Erik Sveberg Dietrichs [b,a,*], Timofei Kondratiev [a], Torkjel Tveita [a,c]

[a] Anesthesia and Critical Care Research Group, Institute of Clinical Medicine, UiT, The Arctic University of Norway, 9037 Tromsø, Norway
[b] Department of Research and Education, Norwegian Air Ambulance Foundation, 1441 Drøbak, Norway
[c] Division of Surgical Medicine and Intensive Care, University Hospital of North Norway, 9019 Tromsø, Norway

ARTICLE INFO

Article history:
Received 19 June 2014
Accepted 2 September 2014
Available online 16 September 2014

Keywords:
Accidental hypothermia
Therapeutic hypothermia
Milrinone
Rewarming
Rewarming shock
PDE3 inhibitor
Cardiovascular support

ABSTRACT

Background: Rewarming from hypothermia is often complicated by cardiac dysfunction, characterized by substantial reduction in stroke volume. Previously we have reported that inotropic agents, working via cardiac β-receptor agonism may exert serious side effects when applied to treat cardiac contractile dysfunction during rewarming. In this study we tested whether Milrinone, a phosphodiesterase III inhibitor, is able to ameliorate such dysfunction when given during rewarming.
Methods: A rat model designed for circulatory studies during experimental hypothermia with cooling to a core temperature of 15 °C, stable hypothermia at this temperature for 3 h and subsequent rewarming was used, with a total of 3 groups: (1) a normothermic group receiving Milrinone, (2) a hypothermic group receiving Milrinone the last hour of hypothermia and during rewarming, and (3) a hypothermic saline control group. Hemodynamic function was monitored using a conductance catheter introduced to the left ventricle.
Results: After rewarming from 15 °C, stroke volume and cardiac output returned to within baseline values in Milrinone treated animals, while these variables were significantly reduced in saline controls.
Conclusions: Milrinone ameliorated cardiac dysfunction during rewarming from 15 °C. The present results suggest that at low core temperatures and during rewarming from such temperatures, pharmacologic efforts to support cardiovascular function is better achieved by substances preventing cyclic AMP breakdown rather than increasing its formation via β-receptor stimulation.

Introduction

Accidental hypothermia was the main cause of death among passengers of the Titanic, which sank in the North Atlantic Ocean in 1912 [16]. More recent case reports have stated that core temperatures down to 13.7 °C [7] and nearly 7 h of hypothermic cardiac arrest may be tolerated [15]. Upon this knowledge and the fact that the first responding ship arrived to aid the Titanic only 1 h and 50 min after the sinking, a similar catastrophe could possibly have had a better outcome today. Currently, ship traffic and activity in the search for gas and oil in the Arctic areas are increasing [1]. This is leaving large amounts of people exposed to a cold environment with low sea temperatures, far from hospitals capable of rewarming victims of accidental hypothermia. Successful resuscitation of several such victims was recently demonstrated after the Præstø Fjord accident [23]. However, rewarming these patients is often complicated by a potentially fatal cardiac dysfunction with gradual reduction in stroke volume (SV) [17]. The underlying pathological mechanisms are not fully understood, but experimental studies have found dysfunction mainly in the cardiovascular system [17,24].

In order to ameliorate hypothermia-induced cardiac dysfunction, cardioactive drug therapy aimed at elevating low SV seems advisable. The need for such inotropic support during hypothermia is established in surgical procedures on the aorta [3], where patients

Abbreviations: CO, cardiac output; TPR, total peripheral resistance; PDE3, phosphodiesterase 3; SV, stroke volume; G_p, parallel conductance; MAP, mean arterial pressure; LV, left ventricle; $LVdP/dt_{max}$, the maximum rate of LV pressure change; LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVEDP, left ventricle end-diastolic pressure; CI, cardiac index; SW, stroke work.

☆ *Statement of funding:* The Norwegian Research Council supported this study.

* Corresponding author at: Anesthesia and Critical Care Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT, The Arctic University of Norway, 9037 Tromsø, Norway.

E-mail addresses: erik.sveberg.dietrichs@norskluftambulanse.no (E.S. Dietrichs), timofey.kondratiev@uit.no (T. Kondratiev), torkjel.tveita@uit.no (T. Tveita).

http://dx.doi.org/10.1016/j.cryobiol.2014.09.002
0011-2240/

are cooled to temperatures down to 15 °C [14]. The effects of cardiovascular drugs used during hypothermia and rewarming are however not well described. This is reflected by the striking lack of consensus-based guidelines for use of such drugs during rewarming from accidental hypothermia [21]. Several studies in our *in vivo* rat model have shown that dose-dependent inotropic effects of cardiac β-receptor agonists are altered by hypothermia, resulting in lack of ability to elevate SV and cardiac output (CO) [8,10,11,19].

Through binding of sarcolemmal β-receptors in cardiomyocytes, β-receptor agonists exert inotropic effects by increasing intracellular cAMP concentration. The phosphodiesterase III (PDE3) inhibitor Milrinone differs from β-receptor agonists as it increases cAMP through inhibiting the cytosolic enzyme breaking it down. A recent experiment demonstrated that Milrinone elevates SV and CO during cooling to 15 °C [18]. Further, Milrinone also possess vasodilating properties in normothermic conditions [4] and has been used for inotropic support during successful resuscitation from hypothermic cardiac arrest [15]. Use of Milrinone is however also associated with side effects in normothermic acute heart failure patients [5]. Based upon knowledge of altered effects of β-receptor agonists [8,10,11,19] during rewarming in our rat model, it is therefore important to establish whether good inotropic support can be provided through cytosolic strategies like PDE3 inhibition.

To assess whether Milrinone has positive effects on SV and CO during rewarming from stable hypothermia at 15 °C (core temperature), we used our experimental model where spontaneous cardiovascular activity is maintained throughout the temperature protocol.

Materials and methods

Male Wistar rats (233–365 g) were provided by Charles River (Sulzfeld, Germany) and used in the experiments. The rats had a microbiological status according to the recommendation of the Federation of European Laboratory Animal Science Associations. The animals were quarantined for 1 week on arrival. During experiments, housing was provided in accordance with guidelines for accommodation and care of animals (article 5 of European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, Strasbourg, 18.III.1986). Housing conditions for the rats were controlled with temperature and humidity maintained at 21 ± 1 °C and 55 ± 5%, respectively. The ambient temperature in the surgical theatre was also kept at 21 ± 1 °C. The animals were allowed free access to food and water. The experimental protocol was approved by the Norwegian Animal Research Authority and conducted accordingly.

Anesthesia

Anesthesia was induced intraperitoneally by pentobarbital sodium (55 mg/kg) and fentanyl (50 μg/kg), followed by a continuous infusion of 7.5 mg kg^{-1} h^{-1} pentobarbital sodium and 50 mg kg^{-1} h^{-1} fentanyl through an intravenous line in the right jugular vein, extended to the right auricle. The infusion was maintained at all hours in normothermic animals. Infusion in hypothermic animals was terminated at 30 °C during cooling and restarted at the same temperature during rewarming, due to hypothermia-induced anesthesia and reduced drug metabolism. The animals were monitored by toe-pinch for any sign of discomfort so that additional anesthesia could be provided if necessary.

Respiratory support

Animals were placed on the operating table in a supine position. The trachea was opened, and a tracheal tube inserted. All animals had spontaneous and sufficient ventilation at core temperatures >20 °C. Below 20 °C, ventilation was achieved by a volume-controlled small-animal respirator (New England rodent ventilator, model 141, New England Instruments, Medway, MA) using room air.

Core cooling and rewarming

Animals were core cooled and rewarmed by circulating cold or warm water (Thermo stated water bath type RTE-110, Neslab Instruments, Newington, NH) through an U-shaped polyethylene tube placed in the lower bowel. The tube was inserted gently to avoid harm of the intestine. In addition, the double-layered operating table made of hollow aluminum was circulated by temperature-adjusted water. Core temperature was continuously monitored using a thermocouple wire positioned in the lowest part of esophagus, connected to a thermocouple controller (Thermalert Th-5, Bailey Instruments). The hypothermic period (15 °C) lasted 3 h, while cooling and rewarming each lasted 2 h. The rate of core rewarming was chosen based on clinical practice in our university hospital, where fast rewarming has proven successful in hypothermic patients after nearly 7 h of hypothermic cardiac arrest [15] and with core temperatures down to 13.7 °C [7].

Experimental protocol

After surgery, animals were allowed to rest for 45 min before start of experiments. Animals in hypothermic groups were cooled to a core temperature of 15 °C and maintained at this temperature for 3 h, before rewarming to 37 °C. In the normothermic group, animals were held at 37 °C for 5 h. Milrinone (Corotrop, Sanofi-Aventis, Paris, France) or saline was administrated through an intravenous line in the femoral vein, extended to the inferior caval vein. Doses were chosen according to a previous study in the present rat model, using Milrinone during cooling [18].

Normothermic Milrinone group (group 1, n = 6)

Animals received a bolus dose of 0.25 ml Milrinone (0.1 mg/ml) after 3 h of normothermia. This was followed by a continuous infusion of 1.2 ml/h during the last two hours of experiments.

Hypothermic Milrinone group (group 2, n = 7)

Animals were given a 0.25 ml (0.1 mg/ml) Milrinone bolus after 2 h of hypothermia. This was followed by a continuous infusion of 1.2 ml/h given during the last hour of stable hypothermia (15 °C) and during rewarming.

Hypothermic saline control group (group 3, n = 7)

Animals were given a 0.25 ml bolus dose of isotonic NaCl after 2 h of hypothermia. This was followed by continuous infusion of 1.2 ml/h during the last hour of stable hypothermia (15 °C) and during rewarming.

Hemodynamic measurements

Hemodynamic variables were obtained using a Millar pressure–volume conductance catheter (SPR-838, Millar Instruments Inc., Texas). The miniaturized 2.0 French pressure–volume conductance catheter allowed for the assessment of *in vivo* left ventricular (LV) mechanical function in rats [2]. A constant sinusoidal alternating current (0.02 mA root means square at 20 kHz) was applied to drive the conductance catheter, through which changing conductance was used for the measurement of blood volume. Volume measurements in this study included parallel conductance (G_p). Further description of this method and calibration of the catheter is described in detail in a previous report [8]. In addition, mean arterial pressure (MAP) was measured using a pressure transducer connected to a fluid-filled catheter (22G) inserted into the left

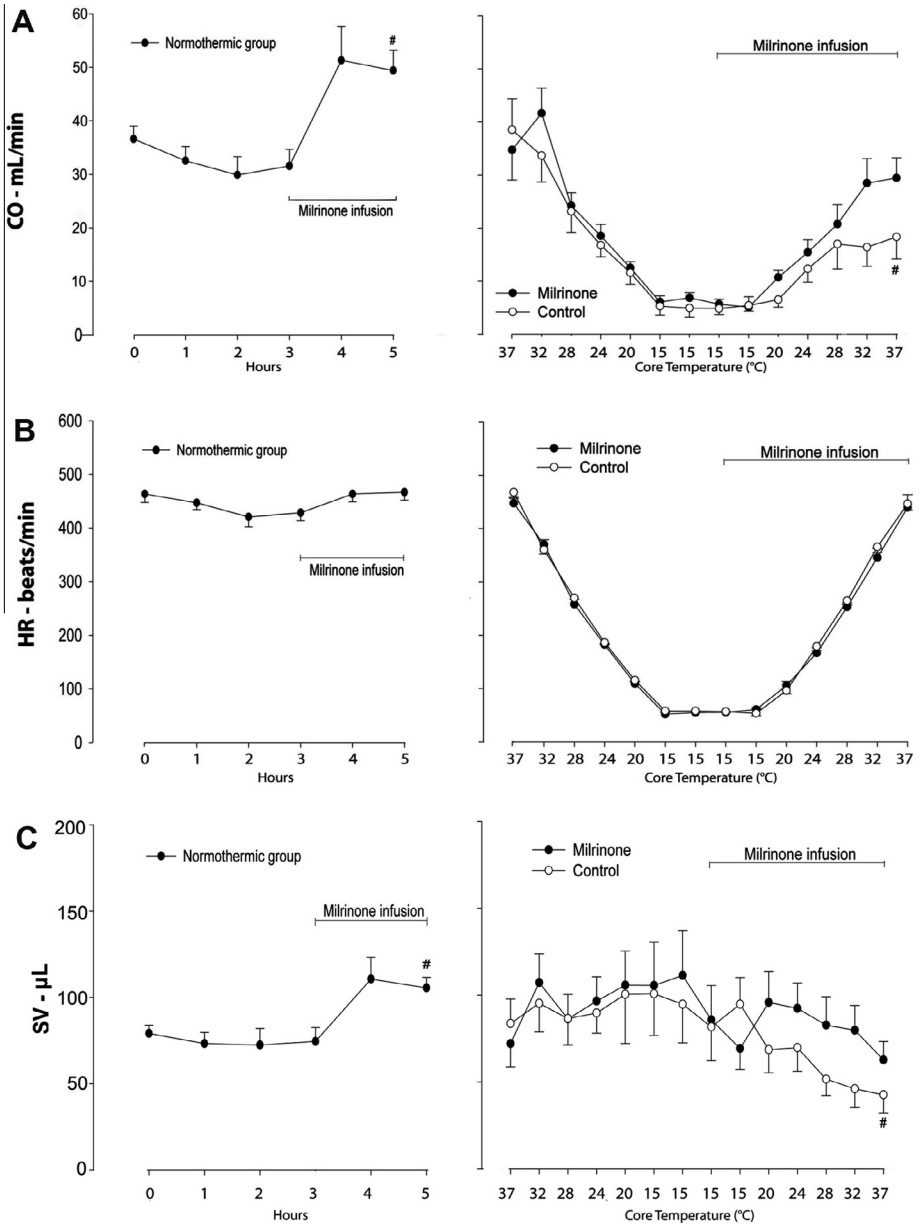

Fig. 1. (A) Cardiac output, (B) heart rate, (C) stroke volume, (D) the maximum rate of pressure change in the left ventricle, (E) total peripheral resistance and (F) mean arterial pressure. Values are mean ± SEM. #Significantly different from baseline ($p < 0.05$). *Significant difference between groups ($p < 0.05$).

femoral artery. This allowed us to monitor peripheral vascular responses during cooling and rewarming. During experiments, hemodynamic measurements were recorded at following core temperatures: 37, 32, 28, 24, 20 and 15 °C.

During cooling, myocardial irritability increases [13]. Therefore we did not find it advisable to adjust the position of the conductance catheter during 3 h at 15 °C. Hence; we were unable to record proper volume signals at this temperature in 6 animals; 4 saline controls and 2 Milrinone treated animals. Due to this, recordings made at 20 °C during cooling and rewarming are used to determine hypothermic values.

Statistical analysis

Results are presented as mean ± SEM. Rats in each experiment were allocated randomly using printed slips of paper that were put into a hat and drawn after surgery to decide the experimental protocol. For within group comparisons with baseline, data were assessed by one-way ANOVA for repeated measurements. We tested for normal distribution of the data with Shapiro–Wilks test and equality of variances with the *F*-test. If the *F* value was greater than critical, data were analyzed using a Dunnett's post hoc test. If normality test failed, repeated measures analysis of variance on ranks was used, followed by Dunnett's post hoc test. Differences between hypothermic groups at same temperatures were tested using a two-tailed, unpaired Student's *t*-test. Differences were considered significant at $p < 0.05$. Data were analyzed and presented using SigmaPlot statistical software version 12.0 (Systware Software, San Jose, CA).

Results

All animals survived the experimental protocol. Except for hypothermia-induced bradycardia and single ectopic ventricular beats, no episodes of arrhythmia occurred during hypothermia or rewarming.

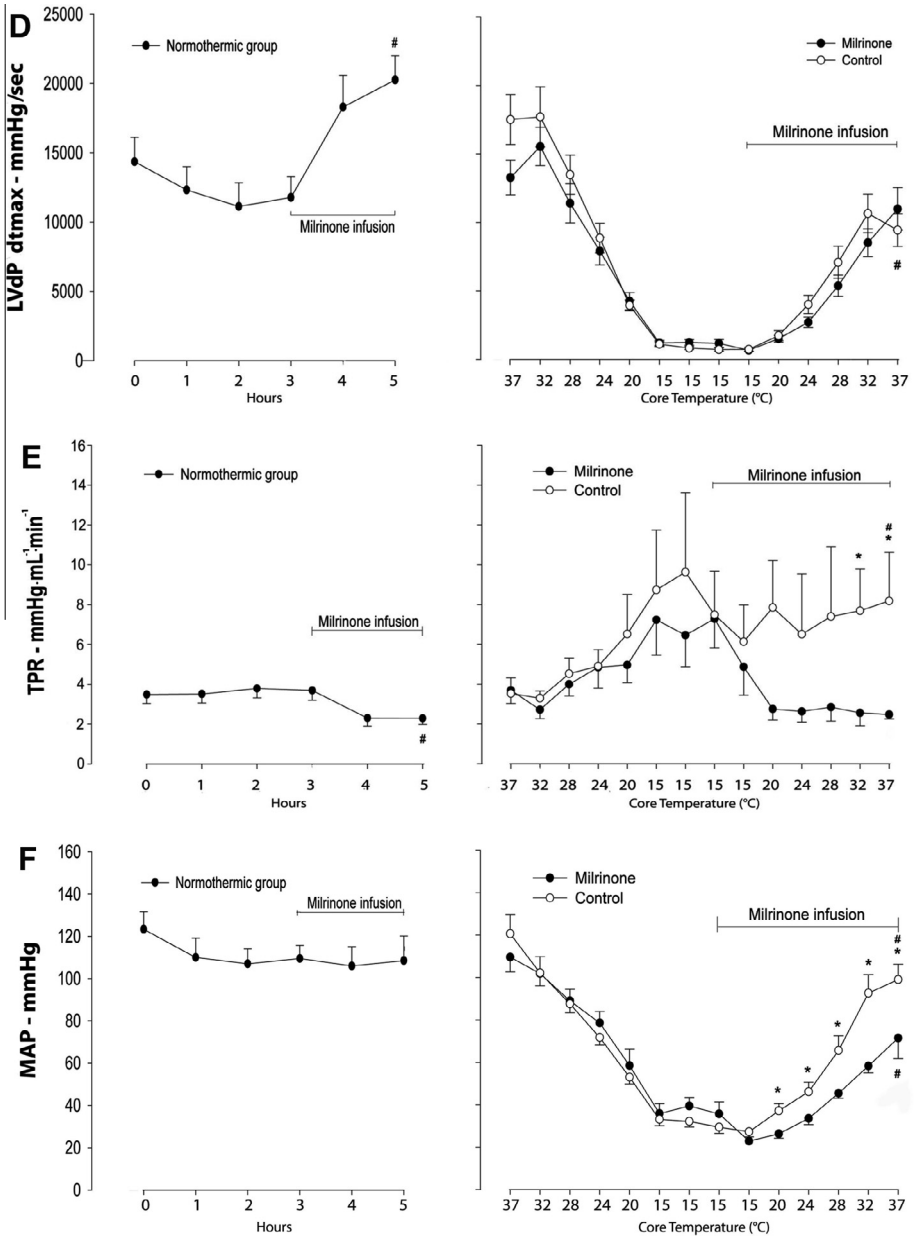

Fig. 1 (*continued*)

Normothermia (37 °C)

Effects of Milrinone infusion in normothermic animals (37 °C for 5 h) (Fig. 1A–F)

After 45 min of stabilization following surgical procedures, recordings were started in the normothermic Milrinone group. Milrinone infusion was started after 3 h at 37 °C. Compared to baseline values, CO, SV and the maximum rate of LV pressure change (LV$dP/dt_{max}$) increased significantly throughout 120 min of Milrinone infusion. Likewise, Milrinone infusion decreased total peripheral resistance (TPR) significantly.

Hemodynamic stability, up to 5 h at 37 °C, has been documented in previous studies using the present intact rat model [24].

Stable hypothermia (20–15 °C)

Saline control and Milrinone group (Table 1, Fig. 1A–F)

At 20 °C, after the stable hypothermia period and after start of saline or Milrinone infusion in the two groups, most indexes of hemodynamic function were significantly reduced from their pre-hypothermic values. Exceptions were increased left ventricle end-diastolic volume (LVEDV) and SV, which showed no difference from baseline. LV end-systolic volume (LVESV) and TPR were only increased in the saline control group. When comparing the groups, MAP and LV end-diastolic pressure (LVEDP) were significantly lower in Milrinone treated animals than in rats receiving saline.

Rewarming (37°C)

Saline control group (Table 1, Fig. 1A–F)

After rewarming saline controls from 15 °C, a statistically significant reduction in parameters of cardiac function had occurred. Posthypothermic values of CO, the correlation between CO and body surface area; cardiac index (CI), SV, stroke work (SW), and LV$dP/dt_{max}$ were all reduced when compared to prehypothermic baseline values. Also LVSP and MAP were reduced after rewarming these animals. In contrast, TPR, LVESV and LVEDP were significantly elevated after rewarming.

Table 1
Additional hemodynamic parameters.

Parameter	Hypothermic group	37 °C	20 °C cooling	20 °C rewarming	37 °C
LVSP, mmHg	Milrinone	134 ± 8	93 ± 10[#]	45 ± 4[#]	95 ± 7[#,*]
	Saline	145 ± 4	93 ± 6[#]	55 ± 8[#]	118 ± 7[#]
SW, mm Hg μL	Milrinone	7958 ± 1442	7787 ± 1137	3686 ± 684[#]	5626 ± 1016
	Saline	9298 ± 1648	5969 ± 1269	2631 ± 788[#]	3676 ± 1022[#]
CI, μL min^{-1} m^{-2}	Milrinone	90 ± 12	34 ± 4[#]	28 ± 4[#]	78 ± 10[*]
	Saline	98 ± 14	29 ± 5[#]	17 ± 4[#]	46 ± 10[#]
LVEDV, μL	Milrinone	289 ± 9	379 ± 26[#]	358 ± 20[#]	349 ± 14[#]
	Saline	375 ± 64	430 ± 60	493 ± 82[#]	438 ± 70
LVESV, μL	Milrinone	223 ± 11	267 ± 33	250 ± 39	284 ± 39
	Saline	330 ± 65	353 ± 72	448 ± 88[#]	421 ± 67[#]
LVEDP, mmHg	Milrinone	4.1 ± 1.8	14 ± 1.8[#]	10 ± 2.2[#,*]	2.6 ± 1.2[*]
	Saline	5.2 ± 1.8	16 ± 3.3[#]	19 ± 3.5[#]	13 ± 4.7[#]
dP/dt_{min}, mmHg/s	Milrinone	−10,517 ± 733	−1772 ± 375[#]	−607 ± 53[#]	−6505 ± 1017
	Saline	−10,939 ± 1001	−1995 ± 473[#]	−786 ± 120[#]	−9839 ± 1472

Values are mean ± SEM.
[#] Significantly different from baseline ($p < 0.05$).
[*] Significant difference between groups ($p < 0.05$).

Milrinone treated group (Table 1, Fig. 1A–F)

Different from saline controls, indexes of cardiac function: CO, CI, SV, SW and LV$dP/dt_{max}$ all returned to within prehypothermic baseline values after rewarming the Milrinone treated animals. Also LVESV and LVEDP returned to prehypothermic levels, while LVEDV was significantly increased. In contrast, LVSP and MAP showed a significant drop when compared to baseline values.

When comparing values after rewarming in the two hypothermic groups, CI was significantly higher in the Milrinone group than in saline controls. In contrast, LVEDP, LVSP, TPR and MAP were significantly lower in rewarmed Milrinone treated animals compared to in saline controls.

Discussion

The present experiment shows that after rewarming from stable hypothermia (15 °C), Milrinone treated animals regained SV and CO to within pre-hypothermic levels. This is in essential contrast to the significant reduction of these variables in saline controls and indicates that inotropic treatment can ameliorate hypothermia-induced cardiac dysfunction during rewarming.

The importance of applying efficient inotropic support in patients during rewarming from low core temperatures is evident as hypothermia-induced cardiac dysfunction is contributing to the high mortality (30%) in victims of accidental hypothermia [17,20]. The present study shows that Milrinone is a promising drug, which ameliorates such hypothermia-induced cardiac dysfunction by elevating SV during rewarming. The ability of Milrinone to provide inotropic support during hypothermia has a therapeutic potential not only limited to the accidental setting, as induced or therapeutic hypothermia is applied in several clinical procedures. During aortic arch surgery, reduction in core temperature to 15 °C is used [14] and exposure to hypothermia in this setting is associated with an increased demand for inotropic support [3]. These patients are cooled below 33–34 °C, temperatures where pre-clinical studies have reported decreased inotropic effects of β-adrenergic drugs [8,19]. The positive inotropic effect of Milrinone is therefore relevant for cardiac support in patients subjected to therapeutic hypothermia as well as in treatment of accidental hypothermia.

During normothermic conditions, both Milrinone [9] and β-receptor agonists provide positive inotropic effects through elevation of cardiac cAMP levels. The reduced effect of β-receptor agonists at temperatures below 33–34 °C [8,19] could be due to mechanisms such as decreased receptor affinity or reduced signal transduction through G-protein coupled β-receptors, which will reduce the ability of β-receptor agonists to increase cAMP. A previous study from our group is in support of such hypothermia-induced alterations in pharmacology, as the selective β-receptor agonist Isoprenaline largely lost the ability to elevate SV in rats cooled below 33 °C [8]. In contrast, Milrinone possess the ability to elevate SV during cooling to 15 °C [18] and during rewarming as demonstrated in the present study. The ability to increase cAMP, independent of β-receptor stimulation, may therefore be one of the features favoring Milrinone over β-receptor agonists during hypothermia and rewarming.

The posthypothermic restitution of SV and CO in Milrinone treated animals to within prehypothermic levels, show the positive inotropic effect of Milrinone to restore systolic function during rewarming. The present study also demonstrates the vasodilating properties of Milrinone by reducing MAP and TPR when infused during rewarming. This is different from effects reported after using the combined α- and β-receptor agonist Epinephrine during hypothermia in the present animal model, as MAP was increased in the presence of failure to elevate SV in rats cooled below 34 °C [19]. This indicates that vascular effects in response to α-receptor stimulation are intact at temperatures where cardiac effects of β-receptor stimulation have largely disappeared. Thus, increased cardiac afterload appears to contribute substantially to the negative effects of Epinephrine during rewarming [19,10,11]. This finding initiated an ongoing study in our group investigating the hemodynamic effects of the vasodilator Nitroprusside, which selectively reduces cardiac afterload during hypothermia and rewarming. A dose inducing vasodilation without reducing SV during normothermia was chosen. Different from restored cardiac function in Milrinone treated animals, preliminary results show a 50% reduction of SV after rewarming with Nitroprusside infusion. This observation is closely related to clinical observations done in hypothermic patients, where occurrence of hypotension during rewarming is recognized as a grave complicating factor [12] and associated with increased mortality [22]. Thus, our preliminary data indicate that cardiac afterload reduction through vasodilation without additional inotropic support is not adequate for ameliorating hypothermia-induced cardiac dysfunction. As observed in the present study, agents facilitating positive inotropic effect in the presence of reduced cardiac afterload seem favorable for cardiac support during rewarming. Afterload reduction does however not appear to be mandatory for elevation of SV in this setting, as demonstrated

by the ability of Dopamine to elevate SV independent of simultaneous effect on MAP during rewarming [6]. Consequently, it is evident that providing efficient inotropic support without concurrent elevation of afterload e.g. through α-receptor stimulation [19,10,11] is the most promising strategy for ameliorating hypothermia-induced cardiac dysfunction. The pharmacologic effects of Milrinone in this setting are favorable, apparent by the ability to provide positive inotropic support both during cooling to 15 °C [18] and rewarming with beneficial reduction of cardiac afterload. Thus, when aiming to ameliorate hypothermia-induced cardiac dysfunction during rewarming, the present study demonstrates that Milrinone has great potential.

Conclusion

The present experiment shows posthypothermic restitution of LV cardiac function in animals treated with Milrinone. This is opposite to previous experiments using β-receptor agonists and indicates that cardiovascular support during hypothermic conditions should avoid β-receptor stimulation. The present findings therefore demonstrate that Milrinone is a promising drug for supporting hemodynamic function during hypothermia and rewarming.

Acknowledgments

We thank Ole Johan Kemi for his advice and Fredrik Bergheim and Knut Steinnes for their technical support.

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