Levosimendan is superior to epinephrine in improving myocardial function after cardiopulmonary bypass with deep hypothermic circulatory arrest in rats

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Objective: To investigate effects of epinephrine and levosimendan on cardiac function after rewarming from deep hypothermia.

Methods: Forty-five male Wistar rats (400-500 g) underwent cardiopulmonary bypass and were cooled to a core temperature of 13°C to 15°C within 30 minutes. After 15 minutes of deep hypothermic circulatory arrest, they were randomly assigned to treatment with levosimendan (12 µg/kg; infusion of 0.2 µg · kg⁻¹ · min⁻¹) (n = 15) or epinephrine (0.1 µg/kg; infusion of 0.1 µg · kg⁻¹ · min⁻¹) (n = 15) or saline as control (n = 10). The rewarming lasted 60 minutes. Systolic and diastolic function was evaluated at different preloads with a conductance catheter, including the slope of the end-systolic pressure–volume relation (ESPVR) and end-diastolic pressure–volume relationship (EDPVR), preload recruitable stroke work, first derivative of left ventricular pressure (+dP/dt), and its relation to end-diastolic volume, as well as the time constant of left ventricular relaxation (Tau) and maximal slope of the diastolic pressure decrement (–dP/dt). Plasma lactate levels were collected.

Results: Stroke volume, ejection fraction and +dP/dt were significantly higher in the levosimendan-treated group than in the epinephrine group. The slope values of preload recruitable stroke work, ESPVR, and the relation of +dP/dt to end-diastolic volume were significantly higher, indicating a better contractility and increased systolic function. –dP/dt was significantly higher in the levosimendan group (3468 ± 320 vs 1103 ± 101 mm Hg/s; *P* < .01). Left ventricular stiffness expressed by EDPVR and relaxation (Tau) were significantly improved in levosimendan-treated group. Plasma lactated concentrations were lower in levosimendan group (2.03 ± 1.27 vs 4.64 ± 1.02; *P* < .05).

Conclusions: Levosimendan has better inotropic and lusitropic effects than epinephrine during rewarming from deep hypothermic circulatory arrest with cardiopulmonary bypass. (*J Thorac Cardiovasc Surg* 2012;143:209-14)

Deep hypothermic circulatory arrest (DHCA) is widely used during repair of the aortic arch and congenital heart defects as a method of cerebral protection. Since the 1980s, when DHCA became widely used, surgical outcome has improved along with survival and cardiac morbidity.¹ Nevertheless, the effect of myocardial ischemia–reperfusion injury combined with hypothermia–rewarming has important clinical implications and remains a significant contributor to perioperative morbidity and mortality.²

Similar to the cardiac surgical setting, hypotension and low cardiac output are common after rewarming from accidental hypothermia, and up to 50% to 80% of patients have

hemodynamic instability.³ Underlying this process, there is an overall myocardial depression, including both systolic and diastolic dysfunction, that may require the use of inotropic drugs.⁴

Clinical guidelines for management of myocardial dysfunction, either in the setting of cardiac surgical interventions or in accidental hypothermia, are still undetermined. Epinephrine is currently used in the treatment of hypothermia-induced cardiac dysfunction.⁵ However, the evidence of efficacy of epinephrine in this setting has been questioned.^{4,6,7}

This study was designed to investigate whether levosimendan, a Ca²⁺ sensitizer, may be effective in improving myocardial dysfunction after rewarming from DHCA and to compare its efficacy with that of epinephrine.

METHODS

Rat Cardiopulmonary Bypass (CPB) Model

After institutional animal care committee approval, 45 male Wistar rats (400-450 g; Harlan, Udine, Italy) housed under standard laboratory conditions were anesthetized (sodium pentobarbital, 30 mg/kg intraperitoneally) and intubated through the oropharynx with a 14-gauge polyethylene tube. They were mechanically ventilated with a rodent respirator (Harvard Apparatus Inc, Holliston, Mass). The tidal volume was 7 mL/kg and the

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Abbreviations and Acronyms

CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
dP/dt	= maximal slope of the systolic pressure increment
dP/	= systolic pressure increment
dt _{MAX}	
dP/dt _{MIN}	= diastolic pressure decrement
EDPVR	= end-diastolic pressure–volume relationship
ESPVR	= end-systolic pressure–volume relationship
EDV	= end-diastolic volume
LV	= left ventricular
MAP	= mean arterial pressure
P-V	= pressure–volume
SV	= stroke volume

respiratory rate was 50 to 60 breaths/min with an air–oxygen mixture (inspired oxygen fraction = 0.5). Ventilation was adjusted to keep an arterial carbon dioxide tension of 35 to 45 mm Hg. Rats were secured supine on a heating board to maintain rectal temperature at 37°C during the surgical procedure before the initiation of CPB. A thermocouple microprobe was inserted into the left femoral artery and advanced into the descending aorta for the measurement of blood temperature. The left femoral artery was cannulated with a heparinized 24-gauge Teflon catheter to monitor systemic arterial pressure and to collect arterial blood for gas analysis. Central cannulation was performed as previously described.⁸ In brief, after complete sternotomy, a venous cannula (a modified 4-hole 16-gauge Angiocath catheter) was advanced into the right atrium using a right trans–superior vena cava approach, allowing excellent drainage. The left common carotid artery was cannulated using an 18-gauge catheter advanced to the aortic arch and connected to the arterial perfusion line for the CPB circuit. Full heparinization (500 IU/kg) was assured after surgical preparation and immediately before CPB initiation to reduce overall blood loss.

CPB was set up as previously described.⁸ The setup consisted of a venous reservoir, a roller pump, a hollow-fiber oxygenator (Sorin, Mirandola, Italy), and a vacuum regulator with an applied pressure of –30 mm H₂O to facilitate venous drainage, all connected by 1.6-mm internal diameter plastic tubing. Total priming volume was 10.5 mL, gas exchange surface was 450 cm², and heat exchange surface was 15.8 cm².

Study Design

CPB was instituted at a flow rate of 120 mL · kg^{–1} · min^{–1}. A core temperature of 15°C to 13°C was achieved over 30 minutes using CPB-assisted cooling. The roller pump was turned off and DHCA, as confirmed by asystole and lack of measurable mean arterial pressure, was maintained for 15 minutes at 13°C to 15°C.

With the reinstitution of CPB, rewarming started at a flow rate of 100 mL · kg^{–1} · min^{–1}. At the beginning of rewarming, rats were randomly assigned to treatment with levosimendan (loading dose of 12 µg/kg, infusion of 0.2 µg · kg^{–1} · min^{–1}) or epinephrine (loading dose of 0.1 µg/kg, infusion of 0.1 µg · kg^{–1} · min^{–1}) or saline as control.

Infusion started at 20°C and was performed until CPB weaning. CPB inflow rate was gradually increased, reaching the full rate of 120 mL · kg^{–1} · min^{–1} at the end of rewarming at 36°C in a period of 60 minutes. Rewarming was assisted by a heating blanket and a heating lamp. The temperature gradient between the CPB circuit and body core

did not exceed 10°C. After full rewarming, the remaining priming volume was reinfused and animals were weaned from CPB. After the experiment, animals were humanely killed by anesthetic overdose.

Measurements

Hemodynamic parameters were collected continuously during the experiments with a 2F Mikro-Tip pressure–volume (P-V) conductance catheter (SPR-838; Millar Instruments, Inc, Houston, Tex) inserted into the right carotid artery and advanced into the left ventricle. Signals were continuously recorded at a sampling rate of 1000 samples/s using a P-V conductance system (MPVS-400; Millar Instruments), stored, and displayed on a personal computer by the PowerLab Chart5 Software System (AD Instruments, Colorado Springs, Colo). With the use of a special P-V analysis program (PVAN; Millar Instruments), heart rate, mean arterial pressure (MAP), maximal slope of the systolic pressure increment (dP/dt) and the diastolic pressure decrement (dP/dt_{MIN}), and time constant of left ventricular (LV) pressure decay (Tau, according to the Weiss method) were computed and calculated. Stroke volume (SV) and cardiac output were calculated and corrected according to in vitro and in vivo volume calibrations using PVAN software.⁹

In addition to the above parameters, LV P-V relations were measured by transiently occluding the inferior vena cava (reducing preload) under the diaphragm by tying a snare suture around the vein at baseline condition and after CPB weaning. The slope of the LV end-systolic P-V relationship (ESPVR), preload recruitable stroke work, and the dP/dt-EDV relation were calculated as load-independent indexes of LV contractility. The slope of the LV end-diastolic P-V relationship (EDPVR) was calculated as reliable index of LV stiffness.⁹

Lactate levels were measured on arterial blood samples collected after the end of CPB-assisted rewarming.

Statistical Analysis

Results are presented as means ± standard error. For between-group comparisons, 1-way analysis of variance was used, followed by an unpaired 2-tailed Student *t* test or paired *t* test to evaluate differences between groups and within groups versus the baseline, respectively.

RESULTS

Forty-five rats were used in this study and randomized into 3 groups. In the control group, 3 animals had ventricular fibrillation during rewarming and 2 had an MAP less than 40 mm Hg after rewarming. In the epinephrine-treated group, 2 rats had ventricular fibrillation during rewarming. These animals were excluded from the data analysis. In the levosimendan-treated groups, there were no arrhythmic episodes and all 15 rats were successfully rewarmed.

There were no differences in baseline hemodynamic parameters among the 3 groups (Figure 1). During hypothermia at 20°C, it was possible to collect hemodynamic data by temporarily turning off the roller pump. Compared with baseline normothermia, during deep hypothermia there was a marked reduction (60%–95%) in most hemodynamic parameters (Figure 1). However, SV was significantly increased (30%) at 20°C. Full cardiac arrest was achieved at 14°C in all animals.

After rewarming, MAP was significantly increased in epinephrine-treated rats compared with control and up to 20% higher than the baseline values. In the

FIGURE 1. Common clinical hemodynamic parameters at baseline normothermia, during hypothermia (recorded by temporarily turning off CPB at 20°C), and after rewarming. Values represent absolute changes (means $\pm$ standard deviations). * $P < .05$; ** $P < .01$. CPB, Cardiopulmonary bypass.

levosimendan-treated group, MAP was significantly higher compared with control but up to 35% lower than baseline values. Heart rate completely recovered after rewarming and was similar to baseline in all 3 groups with a nonstatistically significant elevation in the epinephrine group.

After rewarming, SV was similar to baseline only in levosimendan-treated rats and was significantly higher compared with both the control and epinephrine-treated groups. In the same way cardiac output was significantly improved only in levosimendan-treated rats compared

FIGURE 2. End-systolic pressure–volume (P - V) relationship (ESPVR) and end-diastolic P - V relationship (EDPVR). Original recordings of representative P - V loops were obtained with a P - V conductance catheter system at different preloads during vena cava occlusion and showed differences in ESPVR and EDPVR between epinephrine- and levosimendan-treated rats. The increased slope steepness of ESPVR and decreased of EDPVR in levosimendan indicate improved contractile function and diminished diastolic stiffness, respectively.

FIGURE 3. Maximal slope of the systolic pressure increment (dP/dt_{max}) and end-diastolic volume (EDV) relationship. The relation between dP/dt_{max} and EDV in 1 representative rat from the levosimendan- and epinephrine-treated groups is shown. Note that the slope values were higher in levosimendan-treated than in epinephrine-treated rats, suggesting that systolic performance is improved after levosimendan infusion (A). Maximal slope of the systolic pressure increment (dP/dt_{max}) at baseline normothermia and after hypothermia–rewarming is shown in the control group (black bar), epinephrine group (gray bar), and levosimendan group (white bar). * $P < .05$ versus control; ° $P < .05$ versus epinephrine (B). C and D, Preload recruitable stroke work (PRSW). The relation between stroke work and EDV in 1 representative rat from epinephrine and levosimendan group is shown. Note that slope values were higher in levosimendan rats than in epinephrine rats, suggesting that systolic performance is augmented in levosimendan (C). PRSW is the slope value of the relationship between stroke work and end-diastolic volume (EDV) in the groups of control, levosimendan, and epinephrine. * $P < .05$ versus control; ° $P < .05$ versus epinephrine (D).

with control, although epinephrine showed a clear improvement without reaching significance.

Functional indices derived from P-V analysis at different preloads are less influenced by loading conditions. Figure 2 shows representative original P-V loops registered during transient occlusion of the inferior vena cava after rewarming in epinephrine-treated and levosimendan-treated rats. ESPVR was steeper after levosimendan infusion than after epinephrine infusion, suggesting a better systolic performance after levosimendan infusion during rewarming. This was confirmed by dP/dt_{max} and dP/dt_{max} related to EDV. dP/dt_{max} is a classic contractility parameter, but it is dependent on changes in preload. Analysis of the relation of dP/dt_{max} to EDV allowed a comparison of dP/dt_{max} values of epinephrine-treated and levosimendan-treated rats at a given EDV

(Figure 3). The slope of this relation was steeper in the levosimendan-treated group. Another confirmation came from preload recruitable stroke work (the slope of the linear relation between stroke work and EDV) (Figure 3). The slope was steeper after levosimendan treatment compared with epinephrine treatment, indicating an improved systolic function determined by levosimendan in this setting. Compared with the corresponding control animals, the overall preload recruitable stroke work values were significantly improved (Figure 3).

The diastolic function after rewarming was described by LV relaxation index (dP/dt_{min} and Tau) and stiffness index (EDPVR) (Figure 4). Levosimendan significantly ameliorated LV relaxation compared with control. Epinephrine only improved Tau compared with control although to a lesser extent than levosimendan. The last improvement

FIGURE 4. Indexes of left ventricular (LV) relaxation. Maximal slope of the LV diastolic pressure decrement (dP/dt_{min}) and time constant of LV pressure decay (τ) at baseline normothermia and after hypothermia–rewarming in control group (black bar), epinephrine group (gray bar), and levosimendan group (white bar). * $P < .05$ versus control; ° $P < .05$ versus epinephrine.

of EDPVR compared with epinephrine but the difference was not statistically significant.

The lactate levels were significantly higher after treatment with epinephrine and in the control group than after levosimendan infusion (Figure 5).

DISCUSSION

Whereas moderate hypothermia is a recognized method of myocardial protection in cardiac surgery,^{10,11} deep hypothermia, be it induced as a neuroprotective measure during aortic arch interventions or be it accidental, induces an overall myocardial depression owing to both systolic and diastolic dysfunction.³ Although often transient, more permanent injury in the form of necrosis and apoptosis might occur. Pulmonary dysfunction, which is frequently associated with hypothermia-induced myocardial dysfunction, exacerbates the low cardiac output state.²

Experimental models of deep hypothermia and rewarming confirm and explain this clinical finding.^{10,12} In an experimental animal model of DHCA, LV contractility, relaxation, and afterload were markedly, but transiently, depressed early after reperfusion and mildly depressed late after reperfusion.¹³

FIGURE 5. Lactate plasma levels after rewarming in the 3 groups. ° $P < .05$ versus epinephrine.

The determination of the pathophysiologic mechanisms underlying cardiac dysfunction after hypothermia–rewarming attributes a pivotal role to Ca^{2+} overload and to the paradoxically reduced myofilament Ca^{2+} sensitivity.¹⁴ The phosphorylation of troponin I represents a well-established mechanism for decreased myofilament Ca^{2+} sensitivity. The same phosphorylation could be mediated by phosphokinase A activated by β -adrenergic stimulation.¹⁵

Moreover, cardiovascular effects mediated by β -adrenoceptors are significantly diminished after hypothermia, suggesting that the use of β -adrenoceptor–specific agonist should be reconsidered.¹⁶ Besides, pharmacologic therapy with catecholamines presents substantial limitations because these are associated with elevated myocardial oxygen consumption, arrhythmogenesis, and regional hypoperfusion leading to organ damage.^{17,18}

Levosimendan is a pyridazinone dinitrite derivative belonging to the new inotropic drugs class of Ca^{2+} sensitizer. It presents a positive inotropic effect by sensitizing cardiac troponin C to calcium during systole, thus increasing cardiac performance without increasing myocardial oxygen consumption and with a weak arrhythmogenic effect.¹⁸

To the best of our knowledge, no data have been published about the efficacy of levosimendan in improving myocardial dysfunction after deep hypothermia–rewarming.

This study was conducted on a rat model of CPB previously validated and described.⁸ DHCA and CPB-assisted rewarming reproduced the clinical setting of both cardiac surgery interventions and extracorporeal resuscitation after accidental hypothermia. The results of this study demonstrated that levosimendan treatment during rewarming produced a significant improvement of clinical used parameters of cardiac functions (heart rate, MAP, SV, and cardiac output). In the same manner, more precise parameters derived from P-V analysis and insensitive to preload effect confirmed significantly improved systolic function after levosimendan treatment when compared with epinephrine.

Epinephrine produced an increased MAP without an improvement in SV and an important elevation in lactate levels, which were significant higher than levosimendan. Moreover, levosimendan was superior in improving diastolic function, which was evident on LV relaxation indexes.

Further investigations are needed to validate these results in the clinical setting and to evaluate the cost/benefit ratio in high-risk patients. Nonetheless, on the basis of these findings, use of Ca^{2+} sensitizer drugs, such as levosimendan, seems rational in induced or accidental deep hypothermia.

The clinical experience with levosimendan is limited to weaning from conventional CPB. Its superiority over catecholamines was already demonstrated as postoperative rescue therapy for high-risk patients difficult to wean from CPB.¹⁸⁻²⁰ The hemodynamic data were limited on systolic function and were consistent with results of this study. However, no data exist about effect of levosimendan on diastolic function after CPB.

Finally, some important limitations remain. The animal model does not faithfully reproduce the clinical setting. In addition, inasmuch as only a single dose of epinephrine and levosimendan with a particular treatment regimen (single loading dose at the beginning of rewarming and then continuous infusion from 20°C to complete rewarming) was investigated, one cannot rule out the possibility that different dosages or treatment schemes might have generated different functional outcomes from the one herein. Nevertheless, this particular treatment regimen for epinephrine was deliberately chosen to compare results with prior studies.⁴⁻⁶

CONCLUSIONS

Levosimendan has better inotropic and lusitropic effects than epinephrine during rewarming from experimental DHCA.

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Discussion

Dr Paul M. Kirshbom (Atlanta, Ga). No disclosures. I have just a couple of quick questions. I could not tell from your presentation whether the animals were off bypass when you did your hemodynamic studies at the end or whether they were still on bypass.

Dr Rungatscher. They went through a complete cardiopulmonary-assisted rewarming, until they reached 36°C, then bypass was weaned and they subsequently underwent hemodynamic analysis by vena cava occlusion method.

Dr Kirshbom. So they were off bypass.

Just 1 quick question. Why do you think the lactate was increased given the fact they were on bypass for the entire study and they were off for a very brief period? Obviously, they were on full bypass. Why would the lactate be increased for that very brief period?

Dr Rungatscher. The arterial lactate levels were increased as a result of 15 minutes of deep hypothermic circulatory arrest followed by cardiopulmonary bypass-assisted reperfusion. Results indicated that reperfusion with levosimendan administration produced a better clearance of lactate than both epinephrine and control. Moreover, lactate after epinephrine infusion was even higher than control, suggesting a noncomplete reperfusion of some region of the body because of the vasoconstrictive effect of epinephrine.

Dr Kirshbom. So your pump flows were comparable between groups?

Dr Rungatscher. Yes.