Levosimendan improves brain tissue oxygen levels after cardiopulmonary resuscitation independent of cardiac function and cerebral perfusion

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Research

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Abstract

Background: Prompt reperfusion is essential to rescue ischemic tissue, but in itself represents a key pathomechanism contributing to poor outcome after cardiac arrest. Experimental data suggest levosimendan as a therapeutic drug to limit ischemia-reperfusion injury by improving cerebral microcirculation and thereby reducing neuronal injury. However, recent studies question its effect on cardiac output and cerebral microcirculation in normally pumping hearts. The present study was designed to investigate the influence of levosimendan on hemodynamic parameters, cerebral perfusion, and cerebral oxygenation after cardiac arrest and resuscitation.

Methods: Ventricular fibrillation was induced in anesthetized juvenile male pigs for 7 min, followed by cardiopulmonary resuscitation. After return of spontaneous circulation (ROSC) animals were randomly assigned to levosimendan (12µg/kg, followed by 0.3µg/kg/min) or vehicle (normal saline) treatment for 6 hours. Cerebral oxygen saturation and brain tissue oxygen levels were determined with near-infrared spectroscopy (NIRS) and fluorescence quenching tissue PbtO 2 probes. Cerebral and kidney perfusion were quantified by fluorescent-labeled microspheres and laser-doppler flowmetry.

Results: Compared to vehicle, levosimendan treated animals showed significantly higher brain tissue oxygen levels after ROSC. This effect was not accompanied by changes in cardiac output, cardiac preload and afterload, arterial blood pressure, nor cerebral microcirculation, indicating a local levosimendan-mediated effect in the brain.

Conclusions: Cerebral oxygenation is key to minimizing neurological damage during and after cardiac arrest. Therefore, current concepts aim at improving impaired cardiac output or cerebral perfusion pressure. In the present study we provide evidence that NIRS fails to reliably detect low brain tissue oxygen levels and that levosimendan improves brain oxygen content. Levosimendan may therefore present a promising therapeutic approach to rescue brain tissue at risk in patients after cardiac arrest or other causes of cerebral ischemia or malperfusion such as stroke or traumatic brain injury.

Background

The number of successful resuscitations after cardiac arrest (CA) is increasing over the last decade, whereas survival and discharge rates, as well as long-term outcome have not improved substantially (AHA Report 2013, Heart Disease and Stroke Statistics) [1]. This discrepancy between successful resuscitation and patient outcome therefore requires new therapeutic strategies to achieve the ultimate goal – good neurocognitive function.

Levosimendan is an inodilatator and Ca^{2+}-sensitizer, clinically established for the treatment of acute heart failure [2]. Based on its combination of inotropic and vasoactive characteristics, levosimendan has become a promising agent in the post CA-care. Potential benefits during cardiopulmonary resuscitation (CPR) were addressed in several studies, suggesting increased “return of spontaneous circulation” (ROSC) rates [3], reduced neuronal injury [4], and organ ischemia/reperfusion injury [5]. These effects are

attributed to known mechanisms of action: Ca^{2+}-sensitization and activation of ATP-sensitive K^+-channels in the vascular bed, but also activation of mitochondrial ATP-sensitive K^+-channels in cardiomyocytes [6]. These regulations result in positive inotropy as well as peripheral and coronary vasodilation.

On the other hand, in isolated hippocampal mouse brain slices subjected to mechanical trauma levosimendan reduced tissue injury [7]. After 40 minutes of aortic clamping and consecutive spinal cord ischemia, levosimendan-treated rabbits showed a better neurologic outcome [8]. The results indicate a neuroprotective effect, which cannot be attributed to cardiovascular changes and suggest a direct cellular effect in damaged tissues.

The causal link between myocardial stimulation and the observed protection after cardiac arrest has not been proven yet. This study was designed to determine the significance of the cardiovascular system for the levosimendan-mediated protection in a porcine model of CA, by targeting the effects of levosimendan on global cerebral perfusion, cerebral microcirculation and systemic hemodynamic parameters, and correlating these changes with brain tissue oxygen levels and cerebral oxygen saturation.

Methods

Subjects

After approval by the Federal Animal Care Committee (Landesuntersuchungsamt Rheinland-Pfalz, protocol number 23 177-07/G 13-1-0103), 19 male pigs (body weight: 28.4 ± 3.1 kg; age: two months) were subjected to CA and resuscitation and were randomized thereafter to levosimendan or vehicle treatment. Three animals did not achieve ROSC and were excluded prior to randomization.

Cardiac arrest

Anesthesia was induced with intravenous injections of fentanyl (4 µg/kg) and propofol (3 mg/kg) and was maintained by continuous infusion of fentanyl (8 µg/kg/h) and propofol (8 mg/kg/h). A single dose of atracurium (1.5 mg/kg) was administered prior to endotracheal intubation. Volume-controlled ventilation (AVEA Care-Fusion, San Diego, CA) was conducted (tidal volume 8 mL/kg; positive end-expiratory pressure 5 cmH_2O, FiO_2 = 0.3; inspiration to expiration ratio 1:2; and variable respiration rate to achieve an end-tidal pCO_2 < 6 kPa). Temperature was monitored continuously and maintained constant with a heating blanket.

Via ultrasound guidance five femoral vascular catheters were placed: central venous line, PiCCO cardiac output system (Pulsion Medical Systems, Feldkirchen, Germany) and three introducer sheaths for a) a pacing catheter, b) a catheter for microspheres injection placed in the left heart ventricle and c) an arterial pressure catheter placed in the thoracic descending aorta.

After baseline-measurements, CA was induced with a pacing catheter in the right heart ventricle. After ventricular fibrillation (VF), ventilation and general anesthesia were discontinued. Immediately following 7 min of VF, ventilation was started at a rate of 10 min^{-1}, external chest compressions were initiated with a thumping device (LUCAS 2®, Physio-Control Inc., Lund, Sweden) at a rate of 100 min^{-1}, and 0.4 U/kg vasopressin was injected. After 2 min of persisting VF a first defibrillation with 200 J was performed and additional 0.4 U/kg vasopressin was administered. Afterwards, chest compressions were continued for 2 min, followed by a second defibrillation with 360 J. All animals included in this study achieved ROSC after the second defibrillation. ROSC was defined as presence of heart contractions and mean arterial blood pressure (MAP) above 30 mmHg. Immediately after ROSC 30 mL/kg normal saline were given, anesthesia was resumed, and the animals received either 12 µg/kg levosimendan (LEVO) followed by continuous infusion at a rate of 0.3 µg/kg/min or the equivalent fluid volume of normal saline (VEH). Randomization and preparation of the infusion was done by a third party not involved in the experimental setting.

After ROSC, norepinephrine infusion was started at a rate of 0.3 µg/kg/min. If mean arterial blood pressure (MAP) was below 60 mmHg at 5 minutes after ROSC, an additional normal saline bolus (15 mL/kg) was administered. Target MAP was defined as 75 ± 10 mmHg. Further norepinephrine infusion was adjusted accordingly. Normal saline infusion was adjusted to 5 mL/kg/h and additional boluses were injected if global end-diastolic volume index (GEDI) dropped below 20% of baseline values (before CPR).

The investigators were blinded to the experimental groups. Apart from the continuous infusion of levosimendan or vehicle solution, both groups were treated identically (see Fig. 1).

Hemodynamic variables

An arterial thermo-dilution system (PiCCO-System) was used to determine and record blood pressure, cardiac index (CI), global end-diastolic water index (GEDI), intrathoracic blood volume index (ITBI), and systemic vascular resistance index (SVRI).

Brain hemoglobin oxygen saturation

We quantified cerebral oxygen hemoglobin saturation (rSO_2) with a near infrared spectroscopy (NIRS) probe (Adult Soma Sensor, Covidien, Mansfield, MA, USA) placed on the right forehead. The measured values were updated and displayed in five-second intervals with the INVOS™ 5100C Cerebral/Somatic Oximeter (Somanetics Corporation, Troy, MI).

Cerebral tissue oxygen

Brain tissue oxygen ($PbtO_2$) content was determined with an ultrafast fiber-optic, aluminum-jacketed fluorescence quenching pO_2 probe presenting an uncoated ruthenium complex at the tip (Foxy-AL300, Ocean Optics, Dunedin, FL) [9].

A craniotomy (1 × 1 cm) was performed on the left hemisphere, 5 mm apart from the midline and 5 mm behind the coronal suture, allowing the insertion of the probe (diameter 0.5 mm) through and 14 mm below the dura.

Laser-doppler flowmetry (O2C)

Cerebral microcirculation was measured using the O2C system (LEA Medizintechnik, Gießen, Germany). Based on the doppler principle and light spectroscopy, the system is able to measure regional blood flow 8 mm below the surface. The probe was positioned 1 cm lateral of the Foxy-AL300 probe on the intact dura.

Cerebral perfusion by microspheres

Fluorescent-labeled microspheres (15 µm diameter) were applied for measurement of regional organ blood flow [10]. They were injected via catheter into the left ventricle to be distributed throughout the body and become trapped in capillaries. Four different colors were used in a randomized sequence. 1 mL (equaling 10^6 spheres) was injected at baseline (BL, before CPR) and 30 min, 3 h, and 6 h after ROSC. After scarification, brain and kidneys were dissected, and the microspheres were recovered. Fluorescence was determined by high-performance liquid chromatography (HPLC), allowing for a highly sensitive quantification for each tissue as described before [11].

Statistical analysis

All experiments were performed after randomization and experiments and analysis was performed by investigators blinded to group allocation. Prism 8 statistical software (GraphPad, La Jolla, CA) was used to perform the statistical analysis. Prior to analysis, we checked the test assumptions. Due to the limited power in small samples, we did not perform formal goodness-of-fit tests prior to the t test or analysis of variance (ANOVA), but instead relied on the graphical assessment of distribution characteristics. Normality was checked by inspecting the unimodality and symmetry of histograms, as well as by Q-Q plots. The equality of variances was checked by inspecting histograms and standard deviations. To evaluate group differences in repeated measurements from the same animals, repeated measures 2-way ANOVA was applied (factors: treatment and time), followed by Šidák multiple comparisons test. Comparisons between two independent groups were carried out by the Welch-t test. Values of $p < 0.05$ were considered significant. Correlation analysis between brain tissue oxygen level ($PbtO_2$) and cardiac index was performed using Spearman rank correlation coefficient. Data are presented as the mean and standard deviation (mean ± SD).

Results

Experimental setting

Return of spontaneous circulation was achieved in 16 of 19 animals and all animals with ROSC survived the observation period. Before CPR, the experimental groups did not differ in respect to MAP, arterial and central venous oxygenation, lactate, total norepinephrine dose or total amount of fluid infusion. The total length of ischemia and time from VF-induction to ROSC was similar between both groups (LEVO 674 ± 24 sec, VEH 668 ± 18 sec). In all 16 animals, ROSC was achieved after 0.8 U/kg vasopressin injection and second defibrillation.

Blood pressure and heart rate

MAP and heart rate were recorded throughout the experiments and were not different between both groups (Fig. 2A, B). The vasopressor dose and normal saline volume required to maintain the target MAP were not significantly different between the groups (fluid balance: LEVO: 33 mL/kg, VEH: 30 mL/kg; norepinephrine dose: LEVO: 0.15 µg/kg/min, VEH: 0.22 µg/kg/min) (Fig. 2C, D).

Cardiac index

To determine the influence of levosimendan on post-CPR myocardial dysfunction, cardiac index (CI) was quantified by thermo-dilution technique and normalized to the body weight. As expected in animals without preexisting cardiovascular pathologies, CI was only temporarily impaired promptly after ROSC and recovered within 30 minutes to pre-arrest baseline values (LEVO: 138 mL/min/kg; VEH: 124 mL/min/kg; Fig. 2E) and without differences between both groups.

Influence on serum lactate

As a marker for global tissue ischemia, serum lactate (Fig. 2F) increased noticeably 30 minutes after ROSC from normal baseline values (LEVO: 0.9 mmol/L; VEH: 0.85 mmol/L) to 7.7 mmol/L (LEVO) and 7.0 mmol/L (VEH). In the further course, lactate returned to baseline levels within 6 hours and were not significantly different between the groups.

Global parameters of cardiac preload and afterload

Global End-Diastolic water Index (GEDI, Fig. 3A) and the IntraThoracic Blood volume Index (ITBI, Fig. 3B) describe changes in the volume status at the end of the diastole and the estimated blood volume in the thorax. Both were used as parameters for the cardiac preload. Systemic Vascular Resistance Index (SVRI) was determined as parameter for the cardiac afterload (Fig. 3C) and to describe the influence of levosimendan on the vascular resistance. All three parameters were not influenced by the treatment.

Cerebral perfusion and cerebral oxygenation

To determine changes in cerebral perfusion, we used two independent techniques: before and 30 min, 3 h, and 6 h post ROSC total cerebral blood flow (CBF) was measured with fluorescent microspheres (Fig. 4A) and brain cortical blood flow was determined by O2C (Fig. 4B). To compare cerebral perfusion with the perfusion in other organ systems, at these time points the total blood flow in the kidney was quantified as

index organ (Fig. 4C). To correct for interindividual variations, all parameters were normalized to the individual baseline levels obtained prior to CA. Total cerebral perfusion (Fig. 4A) was stable during the experiments and not influenced by levosimendan. In contrast to the total cerebral perfusion data, regional cortical blood flow (Fig. 4B) decreased significantly to 72% of baseline (VEH) and 63% of baseline (LEVO) after ROSC and returned to baseline values at 3 h and 6 h post ROSC. In contrast to the cortical cerebral perfusion and similarly to the total brain perfusion data, kidney perfusion data did not show any differences between levosimendan and vehicle treatment (Fig. 4C).

Cerebral oxygenation

To determine changes in cerebral oxygenation, two independent techniques were used to quantify this parameter. We measured the cortical cerebral hemoglobin oxygen saturation (rSO_2) by near-infrared spectroscopy (NIRS, Fig. 5A) and the $PbtO_2$ in the frontal cortex by real-time O_2 fluorescence quenching (Fig. 5B). To avoid injury to the dura mater before CA and CPR and to prevent mechanical brain tissue injury during CPR procedure, we did not attempt to place the brain tissue probes before CPR and performed the placement of the Foxy-probe immediately after ROSC. To maintain optimal blood oxygenation, ventilation was adjusted as described above. Settings were confirmed by arterial blood gas analysis. Using these settings, German landrace pigs show typically a $PbtO_2$ of 39.8 mmHg [12].

rSO_2 was not altered by the treatment with levosimendan (Fig. 5A). In contrast to the NIRS readings, $PbtO_2$ was significantly lower at 30 minutes after ROSC. The changes of $PbtO_2$ are in line with the changes of the cortical perfusion at 30 minutes after ROSC. While cortical perfusion was not improved by levosimendan, $PbtO_2$ was significantly higher in the LEVO group at 30 minutes (LEVO: 66.0 ± 24.1 mmHg vs. VEH 34.1 ± 17.4 mmHg, $p = 0.0227$), as well as 3 hours (LEVO: 53.9 ± 14.3 mmHg vs. VEH 29.9 ± 13.2 mmHg, $p = 0.0151$) after ROSC (Fig. 5B). This levosimendan-mediated increase of $PbtO_2$ is independent of CI (Fig. 5C) in levosimendan-treated animals – all showing normal $PbtO_2$, whereas $PbtO_2$ correlates with CI in vehicle-treated animals ($r = 0.6464$, $p = 0.011$). Although mean $PbtO_2$ was in the normal range (25–50 mmHg) in both treatment groups, only some vehicle treated animals showed pathologically low $PbtO_2$ (Fig. 5C).

Discussion

This is the first report that levosimendan directly improves cerebral oxygen levels after global cerebral ischemia-reperfusion injury without improving CI or improving brain tissue perfusion.

After resuscitation, a complex series of events begins during reperfusion, leading to secondary brain damage [13]. The beneficial effects of levosimendan were subject of different studies [14] showing increased ROSC-rates [3, 15], and less post-resuscitation myocardial dysfunction [16], brain injury [4], and kidney ischemia/reperfusion injury [17]. All these positive effects were attributed to enhanced cardiac output [14] or CBF [4] as underlying mechanism. In contrast to this assumption, levosimendan did not improve CI, hemodynamic parameters nor cortical perfusion. Our study confirms data from healthy pigs

without signs of left-ventricular dysfunction showing that levosimendan does not enhance cardiac function [18].

There is a growing body of evidence for a neuroprotective mechanism, which is independent of any cardio-circulatory effect. Following transient spinal ischemia, levosimendan has been shown to ameliorate neurological damage [8], as well as reperfusion injury in a rat middle cerebral artery occlusion model [19] without affecting systemic hemodynamic parameters. In an in vitro model of traumatic brain injury, levosimendan reduced secondary tissue injury [7].

We show that levosimendan improves $PbtO_2$ (2-fold) 30 minutes after CA without influencing perfusion on the micro- or macrocirculatory level. This uncoupling between CBF and tissue oxygenation is highly relevant, since cerebral oxygenation is considered to be directly dependent on cerebral flow. Interestingly, tissue oxygenation in the buccal mucosa was also improved by levosimendan compared to norepinephrine in a rat model of septic shock without major changes in microcirculation and general hemodynamics [20]. We are convinced that our data set is highly reliable since very exact methods were used to measure tissue oxygenation [9], and tissue perfusion, such as the gold standard fluorescence microspheres method, laser-doppler flowmetry and NIRS [21].

In summary, cardiac output, cerebral perfusion and tissue oxygenation data indicate that levosimendan most likely acts at the cellular level by e.g. improving mitochondrial function. The present results could be the missing link between in vitro and in vivo studies. A putative mechanism of action is the activation of mitoK_{ATP} [22]. Levosimendan has also been shown to interact with hydrophobic targets of the respiratory chain complexes, lowering the function of the respiratory chain and possibly reducing ischemia/reperfusion injury in subsarcolemmal mitochondria [23].

The selected methods require tissue digestion to liberate the microbeads to accurately quantify perfusion. It was therefore not possible to also perform molecular and histological analysis in brain tissue. Further investigations are required to confirm the role of mitoK_{ATP} and the respiratory chain complex for the observed influence of levosimendan on brain tissue oxygenation. In addition, healthy animals were used in this study, which do not show cardiovascular comorbidity typically found in patients with CA of cardiac origin. The present study therefore more closely resembles the clinical situation of CA due to e.g. hypoxia or hypovolemia.

Conclusion

Cerebral oxygenation is the key to minimizing neurological damage during and after cardiac arrest. We provide evidence that NIRS fails to reliably detect low brain tissue oxygen levels and that levosimendan improves parenchymal brain oxygen content. This effect was not accompanied with improved cardiac output or cerebral perfusion. Our data therefore suggest a direct levosimendan-mediated at the cellular level. Levosimendan may therefore present a promising therapeutic approach to rescue brain tissue in patients with acute critically low tissue oxygen levels after CA, stroke, or traumatic brain injury.

Abbreviations

BL
baseline
CA
cardiac arrest
CBF
cerebral blood flow
CI
cardiac index
CPR
cardiopulmonary resuscitation
GEDI
global end-diastolic volume index
HPLC
high-performance liquid chromatography
ITBI
intrathoracic blood volume index
LEVO
levosimendan
MAP
mean arterial blood pressure
NIRS
near infrared spectroscopy
PbtO2
brain tissue oxygen
ROSC
return of spontaneous circulation
rSO2
cerebral oxygen hemoglobin saturation
SVRI
systemic vascular resistance index
VEH
vehicle solution
VF
ventricular fibrillation

Declarations

Ethics approval and consent to participate

Experiments were approved by the Federal Animal Care Committee (Landesuntersuchungsamt Rheinland-Pfalz, protocol number 23 177-07/G 13-1-0103).

Consent for publication

The manuscript does not include details, images, or videos relating to an individual person.

Availability of data and materials

All datasets generated and analyzed during this study are kept in the Dept of Anesthesiology, Medical Center of the Johannes Gutenberg-University and are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AGB, SCT, RFK and EKH designed the studies. AGB, JK, AZ, TL and NK conducted the experiment and data collection. BD, SM, KM, AH and NK processed and analyzed tissue for microspheres measurements. AGB and SCT analyzed the data and wrote the manuscript. SCT and EKH reviewed the manuscript and gave final approval for publication.

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Figures

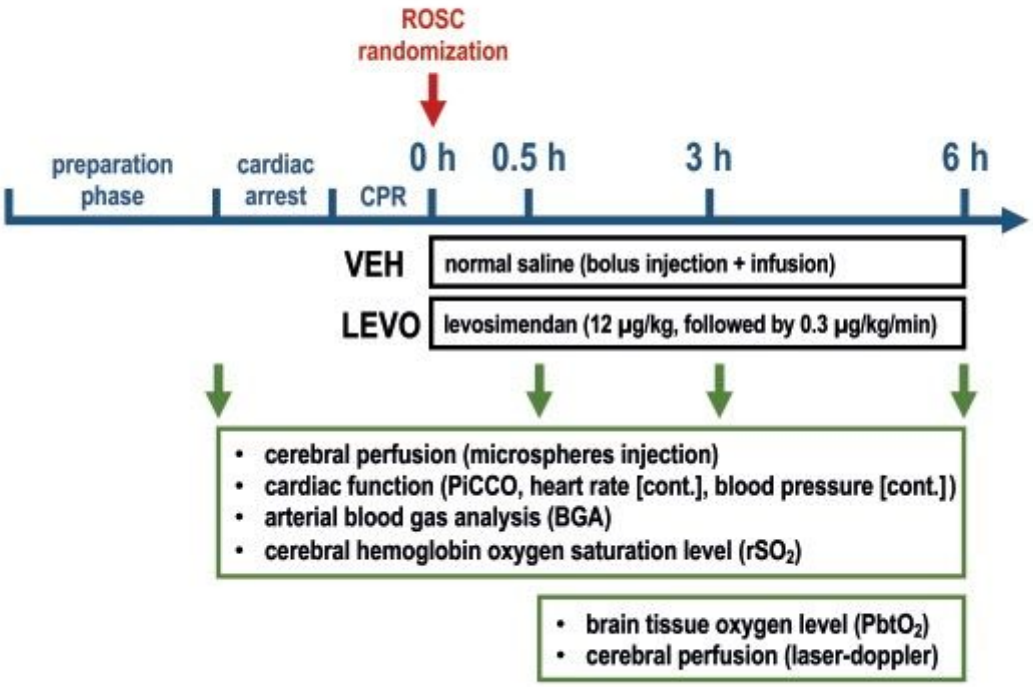

Figure 1

Experimental protocol.

Figure 2

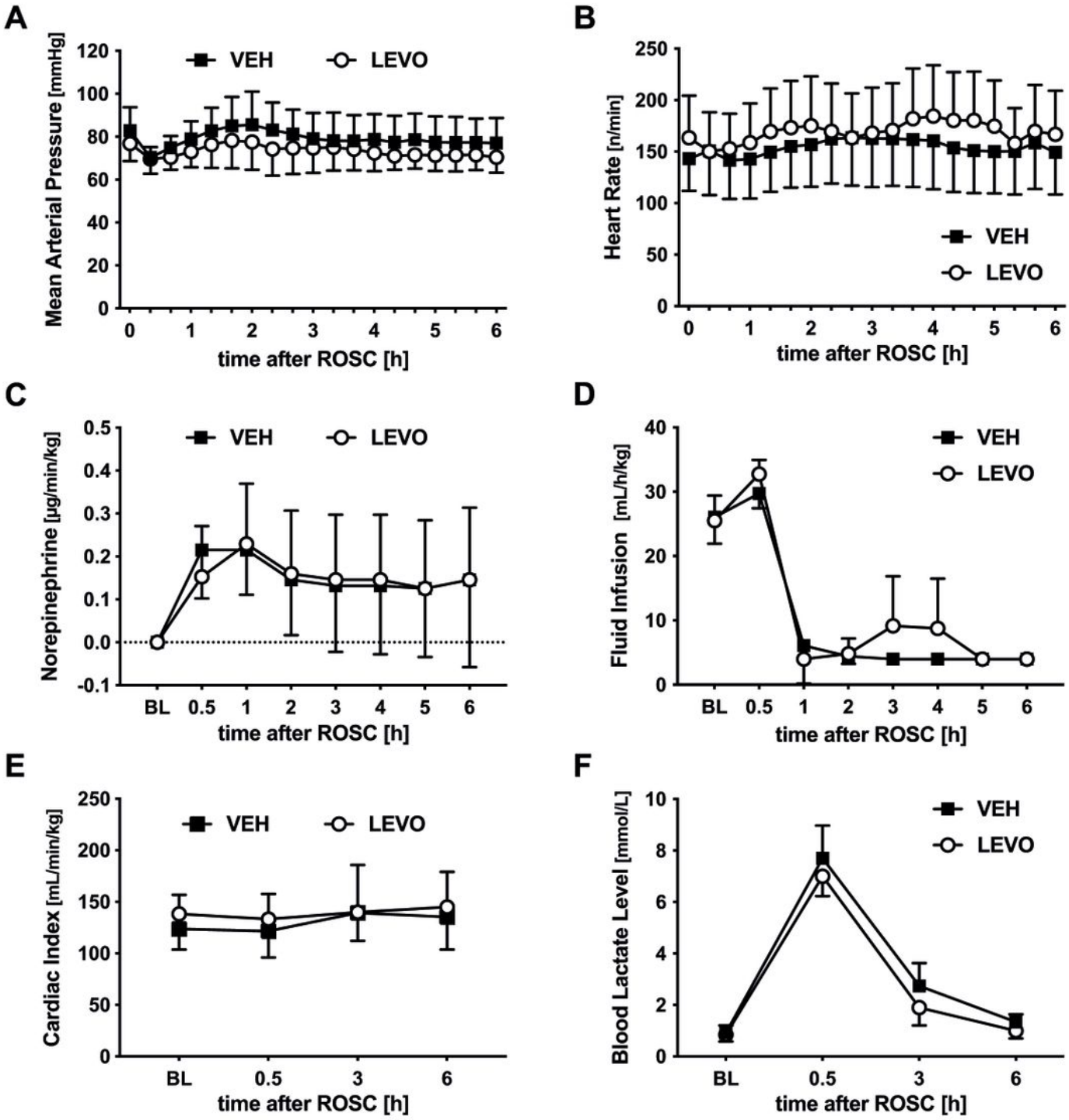

Figure 2

Cardiac index, mean arterial pressure, and key experimental parameters To determine the influence of cardiac arrest and levosimendan on key cardiovascular parameters and the post-CPR management, mean arterial blood pressure (MAP, A) and heart rate (B) were recorded before and after ROSC. MAP was maintained with (C) norepinephrine and (D) normal saline infusion. (E) As a general marker for cardiac function cardiac index was determined before and 0.5, 3 and 6 hours after ROSC using the PiCCO-system.

(F) As a general marker for tissue hypoxia blood lactate was quantified at the same time points. Levosimendan did not influence any parameter compared to vehicle treatment. BL=baseline; VEH=vehicle; LEVO=levosimendan. Statistics: RM two-way ANOVA followed by Šidáks multiple comparisons test; data are presented as the mean ± SD.

Figure 3

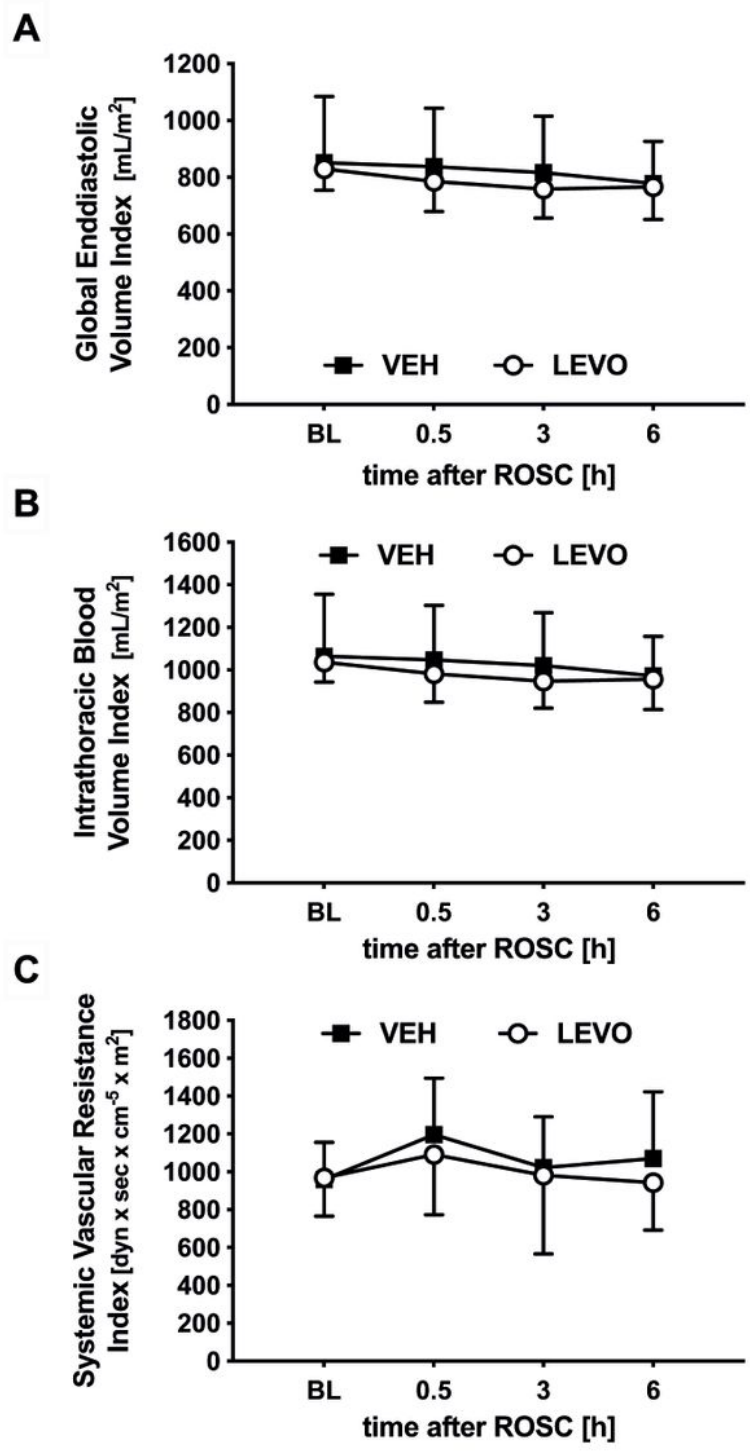

Figure 3

Surrogate parameters for cardiac preload and afterload. (A) Global Enddiastolic Volume Index and (B) Intrathoracic Blood Volume Index as surrogate parameter for cardiac preload were determined using the PiCCO System before and 0.5, 3 and 6 hours after ROSC to investigate changes in the diastolic volume filling and diastolic function after cardiac arrest and levosimendan treatment. (C) To determine the influence on the cardiac afterload the Systemic Vascular Resistance Index was recorded. Cardiac arrest and levosimendan did not influence any parameter at the selected time point. BL=baseline; VEH=vehicle; LEVO=levosimendan. Statistics: RM two-way ANOVA followed by Šidáks multiple comparisons test; data are presented as the mean ± SD.

Figure 4

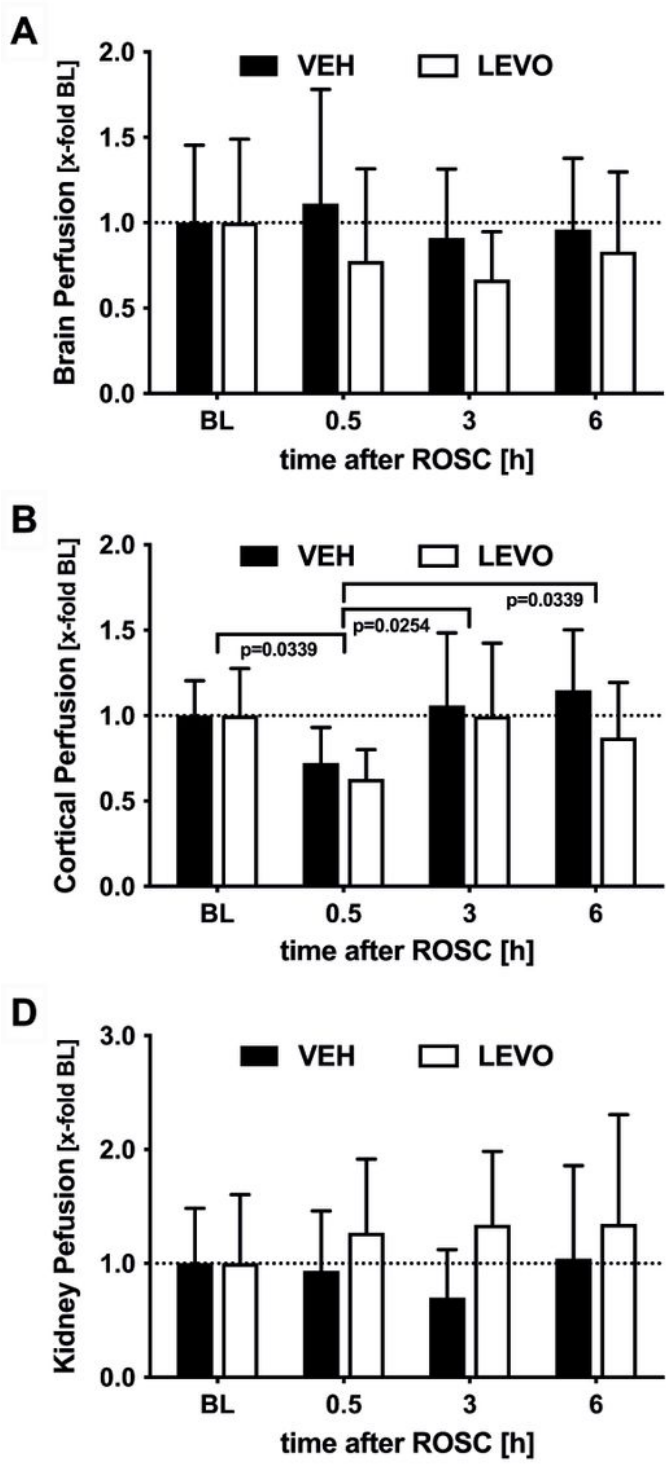

Figure 4

Cerebral perfusion. (A) Global cerebral blood flow was determined before and 0.5, 3, and 6 hours after ROSC using fluorescent microspheres and values were normalized to baseline values to correct for interindividual variations. (B) Cortical blood flow was measured with an epidural laser-Doppler probe. (C) To show systemic perfusion the kidney was selected as index organ and renal blood flow was measured using fluorescent microspheres. Whereas total brain perfusion and renal perfusion was not influenced by

cardiac arrest or by levosimendan treatment, brain cortical perfusion was significantly impaired 30 minutes after cardiac arrest and returned to baseline levels at later time points. BL=baseline; VEH=vehicle; LEVO=levosimendan. Statistics: RM two-way ANOVA followed by Šidáks multiple comparisons test; data are presented as the mean ± SD.

Figure 5

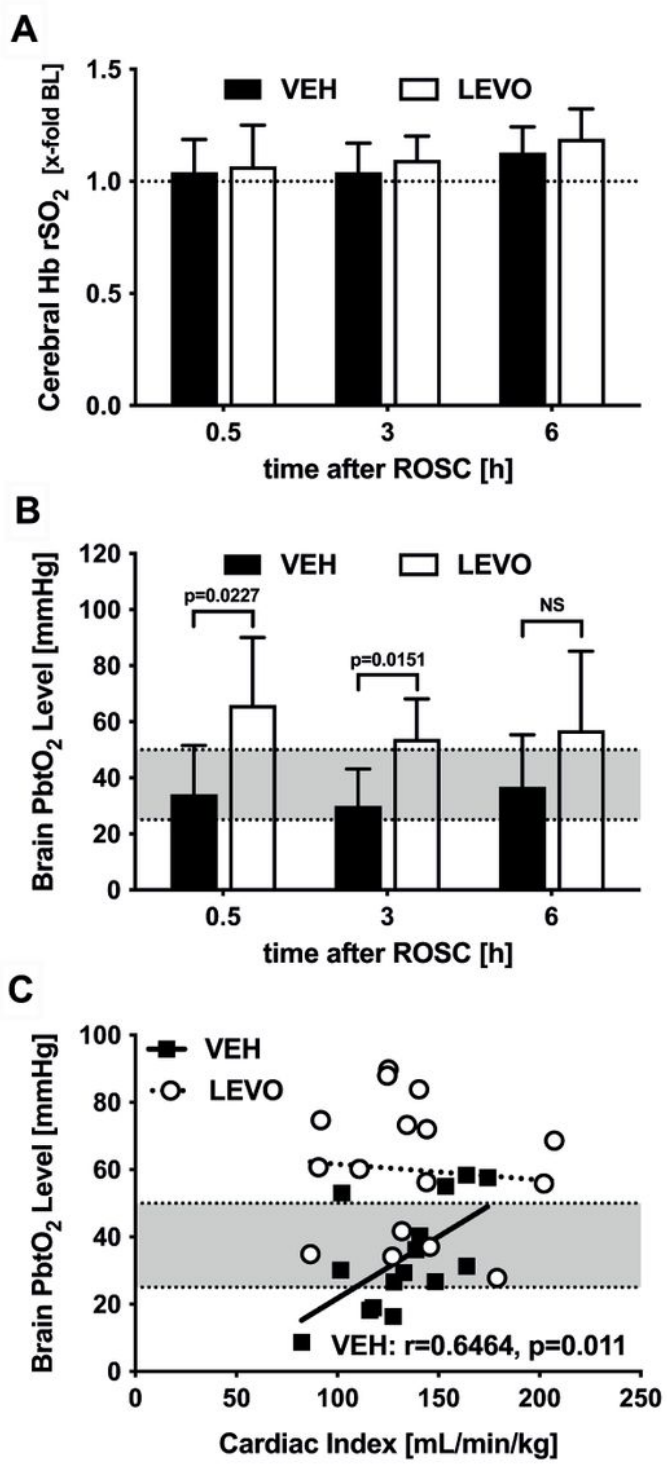

Figure 5

Cerebral tissue oxygenation. (A) Brain oxygenation was determined non-invasively by quantification of brain hemoglobin (Hb) oxygen saturation (rSO2) before and 0.5, 3, and 6 hours after ROSC. Due to high interindividual differences readings were normalized to baseline. rSO2 was not altered after cardiac arrest and not different between groups. VEH=vehicle; LEVO=levosimendan. Statistics: RM two-way ANOVA followed by Šidáks multiple comparisons test; data are presented as the mean ± SD. (B) In addition, brain tissue oxygen (PbtO2) was measured with a Foxy-probe at 14 mm below the dura in the left hemisphere at 0.5, 3, and 6 hours after ROSC. Levosimendan-treated animals showed significantly higher tissue oxygen at 30 minutes and 3 hours after ROSC. Normal PbtO2 range [25-50 mmHg] is illustrated by a grey area. Statistics: Welch-t test; data are presented as the mean ± SD. (C) Correlation analysis between brain tissue oxygenation (PbtO2) and cardiac index (CI) shows a significant association between cardiac function and brain tissue oxygen in vehicle treated animals, whereas levosimendan-treated animals have all normal PbtO2 and show no correlation between PbtO2 and CI. Normal PbtO2 range [25-50 mmHg] is illustrated by grey area. Statistics: Spearman rank correlation coefficient.