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Lactate infusion improves cardiac function in a porcine model of ischemic cardiogenic shock

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Abstract

Background Cardiogenic shock (CS) is associated with high mortality and medical therapies have failed to improve survival. Treatment with lactate is associated with improved cardiac function which may benefit this condition. Comprehensive hemodynamic assessment of lactate administration in CS is lacking, and the mechanisms underlying the cardiovascular effects of lactate in CS have not yet been elucidated. In this study we aimed to study the cardiovascular and cardiometabolic effects of treatment with lactate in experimental ischemic CS.

Methods In a randomized, blinded design, 20 female pigs (60 kg) were studied. Left main coronary artery microsphere injections were used to cause CS, defined as a 30% reduction in CO or mixed venous saturation (SvO_2). Subjects were randomized to receive either intravenous exogenous lactate or euvolemic, equimolar saline (control) for 180 min. Positive inotropic control with dobutamine was administered on top of ongoing treatment after 180 min. Extensive hemodynamic measurements were obtained from pulmonary artery and left ventricular (LV) pressure–volume catheterization. Furthermore, endomyocardial biopsies were analyzed for mitochondrial function and arterial, renal vein, and coronary sinus blood samples were collected. The primary endpoint was change in CO during 180 min of treatment.

Results Arterial lactate levels increased from 2.4 ± 1.1 to 7.7 ± 1.1 mmol/L ($P < 0.001$) during lactate infusion. CO increased by 0.7 L/min ($P < 0.001$) compared with control, due to increased stroke volume ($P = 0.003$). Notably, heart rate and mean arterial pressure did not differ significantly between treatments. End-systolic elastance (load independent contractility) was enhanced during lactate infusion ($P = 0.048$), together with LV ejection fraction ($P = 0.009$) and dP/dt(max) ($P = 0.041$). Arterial elastance (afterload) did not differ significantly ($P = 0.12$). This resulted in improved ventriculo-arterial coupling efficiency ($P = 0.012$). Cardiac mechanical efficiency ($P = 0.003$), diuresis ($P = 0.016$), and SvO_2 ($P = 0.018$) were increased during lactate infusion. Myocardial mitochondrial complex I respiration was enhanced during lactate infusion compared with control ($P = 0.04$). Concomitant administration of dobutamine on top of lactate resulted in further hemodynamic improvements compared with control.

Conclusions Lactate infusion improved cardiac function and myocardial mitochondrial respiration in a porcine model of CS. The hemodynamic effects included increased CO mediated through stroke volume increase. These favorable cardiovascular effects may benefit patients with CS.

†Nigopan Gopalasingam and Kristoffer Berg-Hansen contributed equally to this work.

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Keywords Cardiogenic shock, Lactate, Cardiac output, Hemodynamics, Cardiometabolic, Mitochondrial function

Introduction

Cardiogenic shock (CS) is a complex and life-threatening clinical syndrome with an in-hospital mortality of 30–50% despite treatment [1]. CS is often caused by ischemia due to myocardial infarction and key pathophysiological features involve impaired cardiac output (CO) causing compromised end-organ perfusion and cardiovascular collapse [2]. Current treatment strategies focus on restoring the compromised hemodynamic condition using vasoactive agents such as inotropes and vasopressors are pivotal, along with mechanical circulatory support in selected patients [2, 3]. However, no medical intervention has improved the survival rate in patients with CS [2, 4]. Hence, an urgent need for new medical treatment options for CS remains.

In CS, circulating lactate often increases as a result of hypoperfusion and increased anaerobic metabolism and is a strong predictor of disease severity and worse clinical outcome in CS [5, 6]. However, the production of lactate is not confined to anaerobic conditions but occurs even in resting state with aerobic conditions, and lactate is metabolized in healthy heart, brain, liver, skeletal muscle, and kidney, though to a lesser degree than during hypoperfusion [7]. In experimental models of cardiac arrest, lactate infusion increases mean arterial blood pressure (MAP) and CO and protects against cardiac and cerebral damage [8]–[10]. Similar hemodynamic effects have been demonstrated in studies of healthy animals [11], healthy adults [12], and in experimental models of septic shock [13]–[15]. Furthermore, lactate infusion increases CO in patients with various cardiac pathologies such as acute heart failure and non-ischemic CS [16–19], while increased myocardial lactate oxidation improves cardiac mechanical efficiency in patients with chronic heart failure [20]. Despite these findings, the underlying cardiovascular and metabolic mechanisms by which lactate exerts its hemodynamic effects remain unclear. Notably, no studies have explored the effects of lactate infusion in ischemic CS, leaving a considerable gap in our understanding of its therapeutic potential in critical care. Therefore, the aim of this study was to investigate the cardiovascular and cardiometabolic effects of lactate infusion in an established model of ischemic CS in human-sized pigs [21, 22]. We hypothesized that infusion of lactate could increase CO during ischemic CS.

Methods

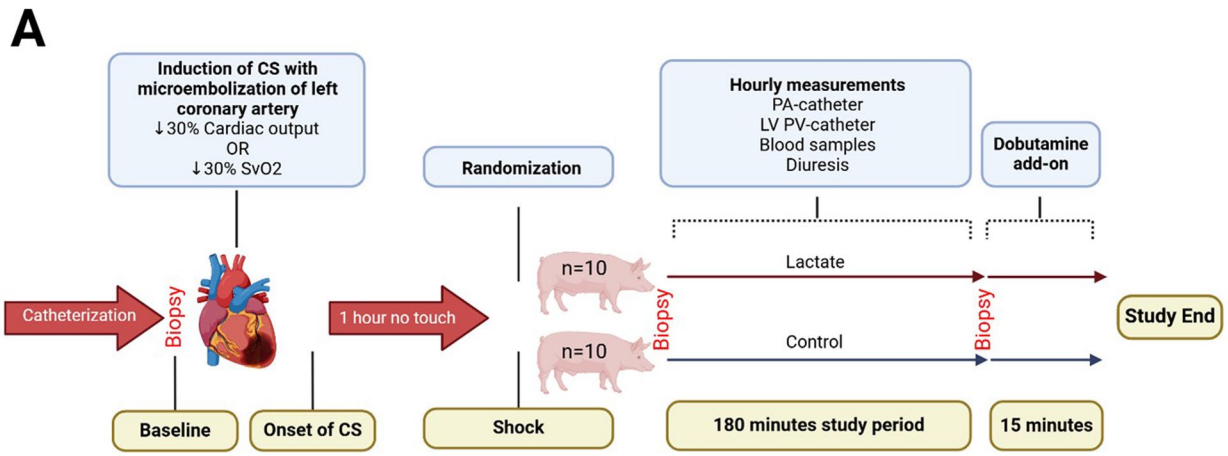
Study design

In this prospective experimental study, female Danish Landrace pigs with an approximate weight of 60 kg were studied. A well-established method was applied to cause CS through repeated slow injections of polyvinyl microspheres (Contour™, Boston Scientific, USA) into the left main coronary artery [22]. Hemodynamic parameters were allowed to stabilize for three minutes following each injection before additional injections of microspheres. Inclusion criteria were a 30% reduction in either CO or mixed venous saturation (SvO_2) relative to measurements in healthy state. Injections of microspheres were repeated until the inclusion criteria were met. These prespecified cutoff values were based on a pilot study in our animal laboratory, demonstrating that further hemodynamic deterioration would require treatment escalation, thus remaining out of the scope of the current study. Pigs that died before study end were replaced. Upon reaching the CS criteria, pigs were subjected to a one-hour no-touch period before initiation of the study interventions.

The study was a randomized, controlled, assessor-blinded study (Fig. 1). The pigs were randomized into two groups (n = 10 per group) using computer-generated randomization. Randomization was performed during the one-hour no-touch period after instrumentation. Pigs received either 2.9 ml/kg/h of 1 molar sodium lactate infusion (lactate) or 2.9 ml/kg/h equimolar, euvolemic matched hypertonic saline (control) for 180 min. At the end of the treatment period, a 15-min infusion of 5 µg/kg/min of dobutamine (Dobutrex, STADA Nordic ApS, Denmark) was infused on top of ongoing infusion with lactate or control to confirm a contractile reserve despite CS. The primary endpoint was defined as; mean change in CO during the 180 min of lactate infusion as compared with control infusion. All hemodynamic parameters, mitochondrial function, metabolites, and other biochemistry were evaluated as mean change during the 180 min of lactate infusion as compared with control infusion.

Animals and ethics approval

The study applied a procedure to minimize stress and increase refinement in the care of the pigs. Initially, pigs received sedation on the farm via intramuscular injection of a commonly used anesthetic mix (Zoletil 50 Vet, Virbac, Denmark). The pigs were intubated and immediately



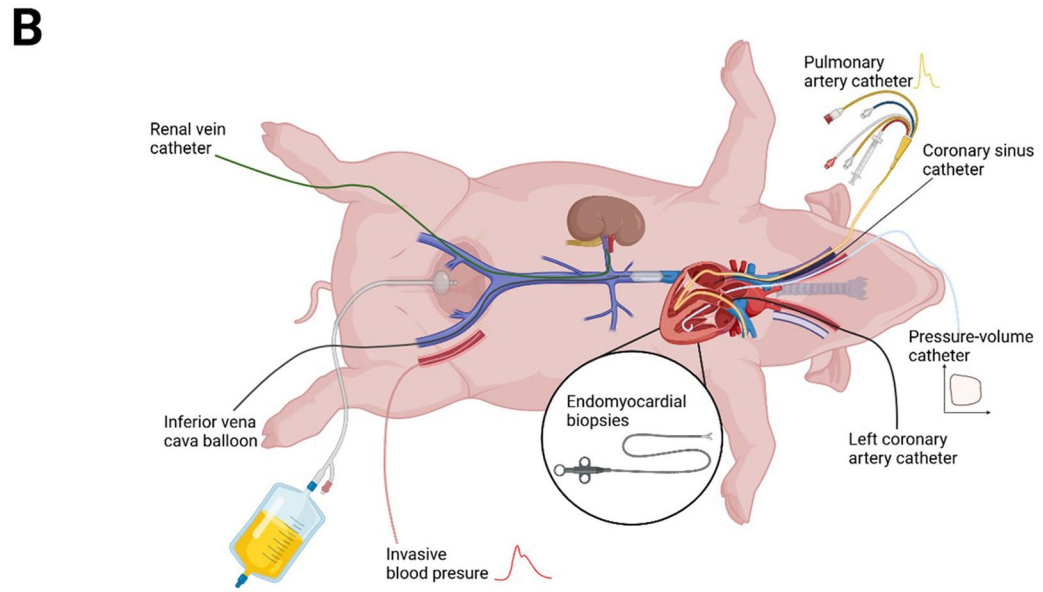


Fig. 1 Study design and animal catheterization. **A** After catheterization cardiogenic shock (CS) was induced with repeated injections of microspheres into the left main coronary artery. CS was considered evident with a 30% reduction in either cardiac output or mixed venous saturation. After onset of cardiogenic shock pigs underwent a one-hour no-touch period to ensure absence of significant worsening or recovery from disease. At baseline, pigs were randomized to receive either a sodium lactate infusion or a tonicity-matched control infusion at a rate of 2.9 ml/kg/h. The primary endpoint was assessed after 180 min of infusion. The study ended following additional 15 min of dobutamine infusion as a positive control. **B** Pigs were catheterized as illustrated. Upon arrival, pigs were intubated and admitted to a ventilator. A Foley catheter was inserted into the bladder before invasive instrumentation. A pulmonary artery (PA) catheter and a coronary sinus catheter were placed through the right jugular vein. A pressure–volume (PV) admittance catheter was inserted into the left ventricle (LV) through the right common carotid artery. A coronary guide catheter was placed into the left main coronary artery through the left carotid artery. An occluding ballon catheter was placed in the inferior cava vein at diaphragm level through a femoral vein. The right renal vein was identified using ultrasound doppler and was catheterized through a femoral vein using a coronary guide catheter. Continuous arterial blood pressure was measured in the left femoral artery. In healthy state, at baseline and after 180 min of treatment endomyocardial biopsies were taken using a biopsy forceps through the left common carotid artery

placed under invasive positive-pressure ventilation. Anesthesia maintenance entailed a continuous infusion of propofol (3.5 mg/kg/h) and fentanyl (15 µg/kg/h). Ventilation parameters included a tidal volume of 8 ml/kg with respiratory rate adjustments to maintain end-tidal CO_2 between 4.5–5.5 kPa. PEEP was set to 5.0 cmH_2O. Prior to baseline measurements, fractional inspired oxygen was adjusted to the lowest level to maintain PaO_2 within 11 to 13 kPa.

The study was conducted after obtaining the necessary authorization from the Danish National Animal Experiment Inspectorate. (*Hemodynamic Optimization with Carbonates, Permit no: 2023–15–0201–01466, issued on 19/06–2023*). The treatment administered and ethical oversight concerning the animals strictly adhered to established animal welfare protocols and regulatory standards mandated by both Danish and European legislation. The methodologies employed and the handling of animals conformed to the guidelines outlined in the EU Directive 2010/63/EU pertaining to animal experimentation. Animal use was supervised by veterinarians, and all facilities and transportation complied with current legal requirements and guidelines. Following the conclusion of the study, all animals were humanely euthanized with a lethal dose of pentobarbital (Euthanimal, Scanvet, Denmark). The study was conducted in accordance with the PREPARE guidelines for study planning and the ARRIVE 2.0 guidelines for comprehensive study reporting.

Preparation of infusion solutions

The one molar sodium-lactate infusion was made by mixing a two molar sodium lactate solution (SODIO LATTATO 2 mEq/ML, Monico, Italy) with isotonic saline (Natriumklorid "B. Braun", B. Braun Medical, Denmark) at a 1:1 ratio producing a solution with 1 mol/L sodium lactate (24.7 g/L of sodium). The control solution was a hypertonic sodium chloride solution with the same amounts of sodium as the intervention solution (24.7 g/L).

Infusions were administered in a peripheral venous catheter using a controlled infusion system (GP Plus Volumetric Pump, BD Alaris, USA). Infusion rates were set to 2.9 ml/kg/h (2.9 mmol lactate/kg/h). This infusion rate was chosen based on pilot studies to decrease the sodium load compared with our previous study while still achieving sufficiently elevated lactate levels [11].

Hemodynamic monitoring

MAP was measured via a femoral artery catheter, and heart rate (HR) was monitored using a three-lead ECG. A pulmonary artery (PA) catheter (Swan Ganz, Edwards Lifesciences, USA) was inserted via the internal jugular vein under pressure guidance, with placement confirmed by fluoroscopy. CO was measured using the bolus thermodilution method with a Vigilance box (Edwards Vigilance VGS), averaged over three measurements with less than 10% variation. Right atrial pressure (RAP), mean PA pressure (mPAP), and PA wedge pressure (PAWP) were recorded hourly. Stroke volume (SV = CO/HR), systemic vascular resistance (SVR = 80 × (MAP-RAP)/CO), pulmonary vascular resistance (PVR = 80 × (mPAP-PAWP)/CO), cardiac power output (CPO = (MAP × CO)/451) [23], and PA pulsatility index (PaPi = [PA pulse pressure]/RAP) were calculated [24]. SvO_2 was measured from the distal PA catheter port using a blood gas analyzer (ABL90 Flex, Radiometer, Denmark). Rate-pressure-product (RPP = [systolic blood pressure] × HR) and coronary perfusion pressure were calculated (CPP = [diastolic blood pressure]–PAWP).

Left ventricular pressure–volume assessment

A pressure–volume (PV) admittance catheter (Transsonic, USA) was advanced into the left ventricle (LV) via the right carotid artery under fluoroscopic guidance and remained fixed throughout the study. PV recordings were pressure-calibrated, then volume-calibrated to SV from the PA catheter, and data were collected during apnea. Recordings were continuously captured in LabChart 8 Pro (AD Instruments, Australia) for blinded analysis. A transfemoral occlusion balloon (Edwards Lifesciences) was placed in the inferior vena cava, and baseline balloon occlusion was used to determine theoretical ventricular volume when no pressure is generated (V_0) [25, 26]. Arterial elastance (Ea) was calculated as the slope between LV end-diastolic volume (LVEDV) and LV end-systolic pressure (LVESP). End-systolic elastance (Ees) was estimated as (Ees = LVESP/ [LVESV-V_0])) and defined as the slope of the end-systolic PV relationship (ESPVR). Ventriculo-arterial coupling (VA coupling) was defined as Ea/Ees. Additional hemodynamic parameters were assessed, including LV end-systolic volume (LVESV), LV ejection fraction (LVEF), maximum rate of LV pressure rise and decay (dP/dt(max) and dP/dt(min), and LV diastolic time constant (tau).

Mechanical energy parameters were calculated as described previously [27]. Briefly, these included stroke work (SW), which was calculated by the LabChart software, potential energy (PE = LVESP × (LVESV-V0)/2), pressure volume area (PVA = SW + PE), cardiac mechanical efficiency (CE = SW/PVA), and cardiac work (CW = PVA × HR).

Left main coronary artery catheterization

The left main coronary artery was catheterized under fluoroscopic guidance using a JL 3.5 catheter (Launcher, Medtronic Inc., USA) via the left carotid artery. The

left anterior descending and left circumflex arteries were identified following contrast injection. The catheter was then secured and utilized for the injection of microspheres into the left main coronary artery. It was removed upon meeting the predefined CS criteria.

Endomyocardial mitochondrial respirometry

A flexible biopsy forceps (JawzTM, Argon Medical Devices, USA) was inserted through the left carotid artery into the LV under fluoroscopic guidance to collect endomyocardial biopsies. Mitochondrial respiratory capacity was measured using the Oxygraph 2 K (Oroboros Instruments, Austria). The substrate protocol included glutamate and malate for complex I respiration, followed by ADP and succinate for maximal respiration through complexes I and II, respectively. Oligomycin was added to assess state 4o leak respiration, and rotenone and antimycin A were used to measure residual oxygen consumption. Our aim was to assess the intrinsic oxidative phosphorylation capacity of the mitochondria. Thus, by bypassing upstream metabolic steps by using this standard protocol for analysis of permeabilized fibers and focusing on complexes I and II, the maximum capacity of the electron transport system rather than the immediate effect of specific in vivo substrates is quantified. Chambers were hyperoxygenated, and measurements were done in duplicate. Detailed protocols are available in Supplemental Material S1.

Coronary sinus and renal vein catheterizations

The coronary sinus was catheterized through a jugular vein using a coronary guide catheter under fluoroscopic guidance. The right renal vein was identified using ultrasound doppler and was catheterized through a femoral vein using a coronary guide catheter under fluoroscopic guidance. Correct positioning of both catheters was ensured using flushes of contrast. The catheters were fixed and left untouched throughout the study.

Biochemistry and fluid balance

Arterial, mixed venous, renal vein, and coronary sinus blood samples were obtained simultaneously at baseline, following CS induction, and every hour during the entire study period. Lactate, glucose, electrolytes, and acid–base parameters (pH, $PaCO_2$, HCO_3^-) were analyzed immediately after sampling (ABL Flex90, Radiometer, Denmark). Free fatty acid (FFA) levels were measured with an enzymatic colorimetric method assay kit (Wako NEFA-HR [2], Wako Chemicals GmbH, Germany). The venous-to-arterial CO_2 tension difference (P(v-a)CO_2) was calculated, with lower values indicating improved peripheral tissue perfusion [28]. Transcardiac and transrenal P(v-a)CO_2 were also calculated. Coronary sinus and renal vein blood samples were also used to measure cardiac and renal venous oxygen saturation (SO_2) and arterio-venous (A-V) differences of O_2, CO_2 and metabolites.

Statistical methods

The standard deviation of CO (primary endpoint), measured using thermodilution in untreated pigs with CS in this experimental model, is 0.4 L/min (unpublished data from our research facility). By enrolling 20 pigs (10 per group), an effect size of 0.6 L/min would be detected with a power of 80% and a two-sided significance level of 5%. Data was visually analyzed for normal distribution with qq-plots. Normally and non-normally distributed variables are presented as mean ± standard deviation (SD) and median with interquartile range (IQR), respectively. Baseline hemodynamic characteristics were compared with CS at timepoint 0 using a paired T-test for normally distributed data or Wilcoxon signed rank test for non-normally distributed data. Continuous data were analyzed using a linear mixed effects model to compare the effect of lactate with the control. Residuals were analyzed for normal distribution using visual evaluation with qq-plots and parameters were transformed using expanded Box-Cox (Yeo-Johnson) transformation formation if necessary. Treatment and time were defined as fixed effects, whereas animals were selected as random effects. The mean treatment effects of lactate infusion versus control through the 180-min infusion period are presented with 95% confidence intervals (CI). We calculated a two-tailed *P*-value. *P*-values < 0.05 were considered statistically significant. Statistical analyses were conducted in the *R* software (Version 4.2.1, Rstudio, PBC) and graphics were constructed using Prism (Version 8.4.2, GraphPad, San Diego, CA, USA) or *R*.

Results

Induction of cardiogenic shock

CS was achieved in a total of 26 pigs. Three pigs died during the no-touch period due to refractory cardiac arrest with ventricular fibrillation prior to randomization. Two pigs died before randomization due to procedure-related irreversible ventricular fibrillation during endomyocardial biopsy sampling. One pig was excluded because it by mistake received a double dose of lactate. All pigs were replaced 1:1 (Supplemental Figure S1). Hence, 20 animals with CS were included for the final analysis. After induction of CS, at the end of the one-hour no-touch period, CO was reduced from 4.2 ± 1.0 L/min at baseline to 2.6 ± 0.7 L/min (38% reduction, $P < 0.001$) and SvO_2 decreased from 58 ± 9 to 34 ± 6% (41% reduction, $P < 0.001$) (Table 1). CPO and MAP were decreased in CS while LV filling pressures (LVEDP and PAWP) were increased, accompanied by

Table 1 Baseline and cardiogenic shock characteristics

	Baseline (N = 20)	Shock (N = 20)	*P*-value
Hemodynamic parameters			
CO, L/min	4.2 ± 1.0	2.6 ± 0.7	**< 0.001**
CI, L/min/m^2	2.7 ± 0.7	1.6 ± 0.4	**< 0.001**
SvO_2, %	58 ± 9	34 ± 6	**< 0.001**
SysBP, mmHg	125 ± 15	94 ± 15	**< 0.001**
DiaBP, mmHg	75 ± 14	57 ± 12	**< 0.001**
MAP, mmHg	93 ± 13	70 ± 12	**< 0.001**
CPO, W	0.87 ± 0.26	0.40 ± 0.11	**< 0.001**
PaPi	3.3 (1.9; 5.1)	1.9 (1.6; 2.3)	**0.002**
SV, mL	71 ± 20	38 ± 11	**< 0.001**
HR, bpm	62 ± 17	75 ± 27	0.078
mPAP, mmHg	24 ± 8	25 ± 6	0.657
RAP, mmHg	6 ± 3	7 ± 3	0.298
PAWP, mmHg	7 ± 2	13 ± 4	**< 0.001**
SVR, dyn/s/cm^5	1756 ± 534	2060 ± 677	0.124
PVR, dyn/s/cm^5	307 (196; 394)	341 (267; 508)	0.648
P(v-a)CO_2, kPa	1.29 ± 0.35	1.85 ± 0.31	**< 0.001**
Pressure–volume parameters			
LVESV, mL	64 ± 10	77 ± 27	0.055
LVESP, mmHg	106 ± 17	81 ± 11	**< 0.001**
LVEDV, mL	144 ± 26	115 ± 37	**0.007**
LVEDP, mmHg	13 ± 5	18 ± 6	**0.007**
LVEF, %	51 ± 8	33 ± 11	**< 0.001**
Ees, mmHg/mL	1.96 (1.83; 2.27)	1.28 (1.01; 1.82)	**< 0.001**
Ea, mmHg/mL	1.57 (1.18; 2.08)	2.48 (1.51; 3.45)	0.114
VA Coupling	0.69 (0.63; 0.90)	1.63 (1.13; 2.29)	**< 0.001**
Cardiac efficiency, %	70 ± 7	49 ± 13	**< 0.001**
Arterial Biochemistry			
Lactate, mmol/L	1.4 ± 0.7	2.5 ± 1.0	**< 0.001**
Glucose, mmol/L	6.6 ± 1.5	6.6 ± 1.9	0.582
Free fatty acids, mmol/L	0.45 ± 0.13	0.44 ± 0.15	0.758

Hemodynamic and pressure–volume parameters in healthy state and at cardiogenic shock baseline (following one-hour no-touch period after reaching prespecified cardiogenic shock criteria) where the first intervention was initiated. Data are expressed as mean ± SD or median (interquartile range). *P*-values indicate paired T-test for normally distributed data or Wilcoxon signed rank test for non-normally distributed data. **Bold** indicates $P < 0.05$

CI Cardiac index, *CO* Cardiac output, *CPO* Cardiac power output, *DiaBP* Diastolic blood pressure, *Ea* Arterial elastance, *Ees* End-systolic elastance (the slope of the end-systolic pressure–volume relationship), *HR* Heart rate, *LVEDP* LV end-diastolic pressure, *LVEDV* LV end-diastolic volume, *LVEF* LV ejection fraction, *LVESP* LV end-systolic pressure, *LVESV* LV end-systolic volume, *MAP* Mean arterial pressure, *mPAP* Mean pulmonary artery pressure, *PaPi* Pulmonary artery pulsatile index, *PAWP* Pulmonary arterial wedge pressure, *P(v-a)CO2* Veno-arterial carbon dioxide difference, *PVR* Pulmonary vascular resistance, *RAP* Right atrial pressure, *SV* Stroke volume, *SVR* Systemic vascular resistance, SvO_2 Mixed venous saturation, *SysBP* Systolic blood pressure, *VA* Ventriculo-arterial coupling (Ea/Ees)

decreased SV, LVEF, and CE. A non-significant increase in Ea was observed whereas Ees decreased, resulting in VA decoupling. Arterial levels of endogenous lactate increased from 1.4 ± 0.7 to 2.5 ± 1.0 mmol/L ($P < 0.001$).

Hemodynamic effects of lactate infusion

Mean lactate levels were 7.7 ± 1.1 mmol/L during lactate infusion compared with 1.7 ± 2.0 mmol/L during control infusion (between-treatment difference: 5.1 mmol/L; 95% CI: 4.4 to 5.8 mmol/L; $P < 0.001$; Fig. 2). Lactate infusion caused an increase in CO by 0.7 L/min (95% CI: 0.4 to 1.0 L/min; $P < 0.001$) compared with control (Table 2, Figs. 2, and 3). SV increased by 7 mL (95% CI: 3 to 11 mL; $P = 0.003$) whereas HR remained similar between treatments ($P = 0.71$). CPO was also increased. SvO_2 increased by 7%-points (95% CI: 2 to 12%-points; $P = 0.018$), accompanied by decreased P(v-a)CO_2 during lactate compared with control, consistent with the increase in O_2 delivery and CO. Also, the accumulated diuresis during the 180-min treatment period was greater in the lactate group than the control group (176 ml [IQR 131–207 ml] vs 102 ml [IQR 97–135 ml]; $P = 0.016$) (Supplemental Figure S2). PVR was decreased ($P = 0.031$), with no significant difference in SVR ($P = 0.28$). No significant between-treatment differences in RPP, MAP, pulmonary pressures, CPP, and PaPi were detected.

Impact of lactate infusion on pressure–volume parameters

The load independent contractility measure, Ees, was increased by 0.28 mmHg/mL (95% CI: 0.02 to 0.53 mmHg/mL; $P = 0.048$) with a concomitant increase in dP/dt(max) ($P = 0.041$) during lactate infusion compared with control infusion. Despite a trend the afterload measure, Ea, did not differ significantly between treatments (− 0.86 mmHg/mL (95% CI: − 1.89 to 0.02 mmHg/mL; $P = 0.121$). Thus, the Ea/Ees ratio decreased significantly by − 0.67 (95% CI: − 1.13 to − 0.21; $P = 0.012$) during lactate infusion compared with control, indicating improved VA coupling. LVEF was significantly improved during lactate infusion by 9%-points (95% CI: 3 to 14%-points; $P = 0.009$), paralleled by decreased LVESV (between-treatment difference: − 15 mL; 95% CI: − 27 to − 2 mL; $P = 0.038$) compared with control infusion. Furthermore, cardiac mechanical efficiency was significantly enhanced by 10%-points (95% CI 4 to 15%-points; $P = 0.003$) during lactate infusion compared with control. No significant changes regarding SW, PE, PVA and CW were observed. Diastolic parameters (dP/dt(min) and Tau) and preload parameters (LVEDP and LVEDV) were not significantly altered by lactate infusion compared with control.

Impact of lactate infusion on transorgan gradients and biochemical parameters

The transcardiac lactate gradient increased by 1.0 mmol/L (95% CI: 0.6 to 1.4 mmol/L; $P < 0.001$) during lactate infusion compared with control. Meanwhile, there were no differences in transcardiac gradients of other

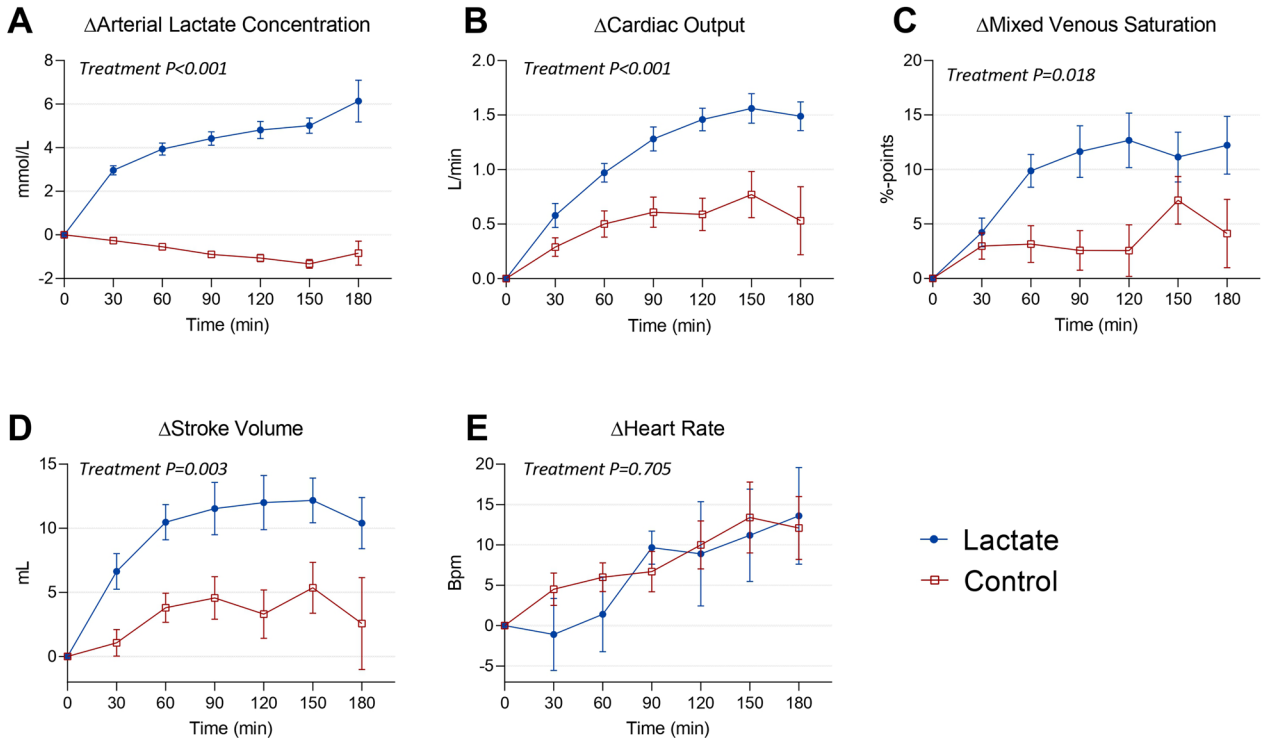


Fig. 2 Temporal changes in arterial **A** lactate, **B** cardiac output, **C** mixed venous oxygen saturation, **D** stroke volume, and **E** heart rate. Data are shown as mean ± SEM. Temporal evolution in cardiac output determinants and arterial lactate concentration from baseline and until 180 min after treatment initiation. *P*-values are derived from the pairwise comparisons assessed using a repeated measurements linear mixed model with time and treatment as fixed effects and each animal as random effects

metabolites, though a trend towards decreased transcardiac gradient of FFAs (−0.13 mmol/L (95% CI: −0.26 to 0.00 mmol/L; $P=0.075$) was observed. Also, there was a trend of increased arterial and coronary sinus SO_2 during lactate compared with control, with no significant difference between treatments in transcardiac oxygen difference. Furthermore, the transcardiac P(v-a)CO_2 difference was significantly decreased ($P=0.012$). No difference in transrenal metabolites, SO_2, or P(v-a)CO_2 was detected.

Whereas arterial sodium levels increased during both treatments, the increase was greater during control infusion (Table 3). Arterial potassium levels were significantly decreased during lactate infusion compared with control while arterial pH and bicarbonate levels increased. Finally, arterial glucose was slightly higher during lactate compared with control infusion (Fig. 4).

Impact of lactate infusion on myocardial mitochondrial function

Mitochondrial respiration linked to complex I, reflecting electron transport chain activity reliant on NADH as the reducing equivalent, was significantly elevated during lactate infusion compared with control ($P=0.040$; Fig. 5 and Supplementary Table S1). In contrast, the increase in oxidative phosphorylation (OXPHOS) capacity, which measures fully coupled respiration through complexes I and II and involves reducing equivalents NADH and $FADH_2$, did not reach statistical significance ($P=0.152$). Additionally, there was no observed difference in state 4o leak respiration between interventions, which reflects proton leak across the mitochondrial membrane without ATP production ($P=0.822$).

Addition of dobutamine on top of intervention

The addition of 15-min dobutamine infusion after 180 min of intervention with lactate or control resulted in significant increases in CO, SV, HR, MAP, Ees, and SvO_2 during both treatments (Supplementary Table S2). The dobutamine-dependent effects on CO ($P=0.112$), HR ($P=0.83$), MAP ($P=0.18$), Ees ($P=0.37$), and SvO_2 ($P=0.564$) were similar during both treatments, while SV increased more during control infusion ($P=0.008$). The cumulative effects (from CS baseline) of dobutamine on top of lactate exhibited improved CO ($P=0.013$), CPO ($P=0.013$), SvO_2 ($P=0.049$), P(v-a)CO_2 ($P=0.030$), LVEF ($P=0.001$), VA coupling ($P=0.022$), cardiac mechanical efficiency ($P<0.001$) and SW ($P=0.006$) compared with dobutamine on-top-off control.

Table 2 Hemodynamic parameters during lactate and control infusions

Variable	Lactate		Control		Linear mixed model	
	Shock (n = 10)	After 180 min	Shock (n = 10)	After 180 min	Effect of lactate vs. control (95% CI)	*P*-value
Hemodynamic pa.rameters						
CO, L/min	2.6 ± 0.6	4.1 ± 0.6‡	2.6 ± 0.7	3.1 ± 0.7	0.7 (0.4 to 1.0)	**< 0.001**
CI, L/min/m^2	1.66 ± 0.37	2.60 ± 0.40‡	1.63 ± 0.46	1.98 ± 0.48	0.42 (0.21 to 0.63)	**< 0.001**
SvO_2, %	32 ± 4	45 ± 7†	36 ± 7	40 ± 11	7 (2 to 12)	**0.018**
MAP, mmHg	70 ± 10	74 ± 8*	70 ± 14	69 ± 19	4 (– 1 to 10)	0.132
CPO, W	0.40 ± 0.08	0.67 ± 0.11‡	0.40 ± 0.14	0.49 ± 0.19	0.14 (0.07 to 0.21)	**< 0.001**
PaPi	2.2(1.8;2.7)	3.0(1.8;3.6)	1.8(1.5;1.9)	2.0(1.7;4.1)	– 0.2 (– 0.0 to 0.4)	0.502
SV, mL	37 ± 11	47 ± 11‡	38 ± 11	41 ± 17	7 (3 to 11)	**0.003**
HR, bpm	78 ± 29	91 ± 26*	72 ± 27	84 ± 26†	– 2 (– 14 to 9)	0.705
mPAP, mmHg	26 ± 6	20 ± 4†	25 ± 7	22 ± 5	– 3 (– 6 to 0)	0.111
RAP, mmHg	7 ± 3	6 ± 2	8 ± 4	6 ± 2	– 0 (– 2 to 1)	0.529
PAWP, mmHg	13 ± 4	11 ± 3	14 ± 5	14 ± 3	– 1 (– 2 to 0)	0.173
SVR, dyn/s/cm^5	2039 ± 762	1371 ± 328†	2081 ± 623	1670 ± 482	– 174 (– 476 to 128)	0.275
PVR, dyn/s/cm^5	424 ± 234	166 ± 81†	369 ± 167	238 ± 80*	– 136 (– 250 to – 24)	**0.031**
P(v-a)CO_2, kPa	1.85(1.68;1.91)	1.15(0.99;1.23)†	1.75(1.65;1.89)	1.48(1.36;1.58)	– 0.41 (– 0.65 to – 0.17)	**0.004**
CPP, mmHg	45 ± 10	47 ± 8	44 ± 14	41 ± 15	3 (– 2 to 7)	0.255
RPP, mmHg*min	7287 ± 2824	8865 ± 2273*	6761 ± 2533	7628 ± 1984*	282 (– 763 to 1327)	0.604
Pressure–volume parameters						
LVESV, mL	80 ± 30	97 ± 34*	74 ± 28	112 ± 42‡	– 15 (– 27 to –2)	**0.038**
LVESP, mmHg	80 ± 11	81 ± 10	81 ± 13	75 ± 22	4 (– 1 to 10)	0.168
LVEDV, mL	118 ± 35	171 ± 53†	112 ± 41	163 ± 63‡	– 8 (– 31 to 15)	0.499
LVEDP, mmHg	18 ± 5	19 ± 8	19 ± 7	19 ± 9	1 (– 2 to 3)	0.647
LVEF, %	31 ± 11	41 ± 14†	36 ± 11	30 ± 9	9 (3 to 14)	**0.009**
Ees, mmHg/mL	1.35 ± 0.57	1.12 ± 0.43	1.71 ± 1.17	0.82 ± 0.32*	0.28 (0.02 to 0.53)	**0.048**
Ea, mmHg/mL	2.36(1.62;3.22)	1.13(0.99;1.63)*	2.60(1.59;3.45)	2.21(0.96;2.66)*	– 0.86 (– 1.89 to 0.02)	0.121
VA Coupling	2.10 ± 1.36	1.42 ± 0.78	1.61 ± 0.84	2.13 ± 0.93	– 0.67 (– 1.13 to – 0.21)	**0.012**
Cardiac mechanical efficiency, %	47 ± 14	56 ± 14†	52 ± 13	42 ± 11*	10 (4 to 15)	**0.003**
PVA, mmHg*mL	5317 ± 1939	8511 ± 2995‡	5205 ± 2024	7074 ± 2999*	436 (– 824 to 1697)	0.509
CW, mmHg*L*min^{-1}	373 ± 99	727 ± 200‡	377 ± 169	580 ± 235‡	56 (– 514 to 164)	0.322
dP/dt(max), mmHg*s^{-1}	1062(925;1112)	1249(1189;1385)†	1070(951;1207)	1154(777;1289)	140 (16 to 264)	**0.041**
dP/dt(min), mmHg*s^{-}	– 1287 ± 172	– 1448 ± 157*	– 1321 ± 304	– 1276 ± 520	– 116 (– 253 to 19)	0.110
Tau, ms	52 ± 11	45 ± 13	57 ± 21	57 ± 29	– 1 (– 9 to 6)	0.796

Hemodynamic parameters at cardiogenic shock baseline and after 180 min of each infusion. Data are expressed as mean ± SD or median (interquartile range)

Pairwise comparisons were assessed using a repeated measurements linear mixed model with time and treatment as fixed effects and each animal as random effects. **Bold** indicates $P < 0.05$ of the linear mixed model analysis

Paired t-test or Wilcoxon signed-rank test was performed comparing mean or median after 180 min of treatment with shock levels in each treatment group. ‡ Indicates $P < 0.001$, † indicates $P < 0.01$ and * indicates $P < 0.05$

CPP Coronary perfusion pressure, *CW* Cardiac work, *RPP* Rate-pressure-product, *PVA* Pressure–volume area, *95% CI* 95% confidence interval. Other abbreviations as in Table 1

Safety

No animals suffered from ventricular arrhythmias during lactate infusion while two animals demonstrated short sequences of pulse bearing ventricular tachycardia during control infusion. Four animals experienced supraventricular arrhythmias with no effect on blood pressures, two during each intervention. Ventilation parameters did not differ between treatments (Supplementary Table S3).

Discussion

We investigated the acute cardiovascular and cardiometabolic effects of lactate infusion in an experimental model of ischemic CS. Lactate improved CO through increased SV in parallel with improved contractility. Several indices of peripheral tissue perfusion also increased wheras MAP remained stable. Notably, the administration of lactate improved VA coupling accommodated by enhanced

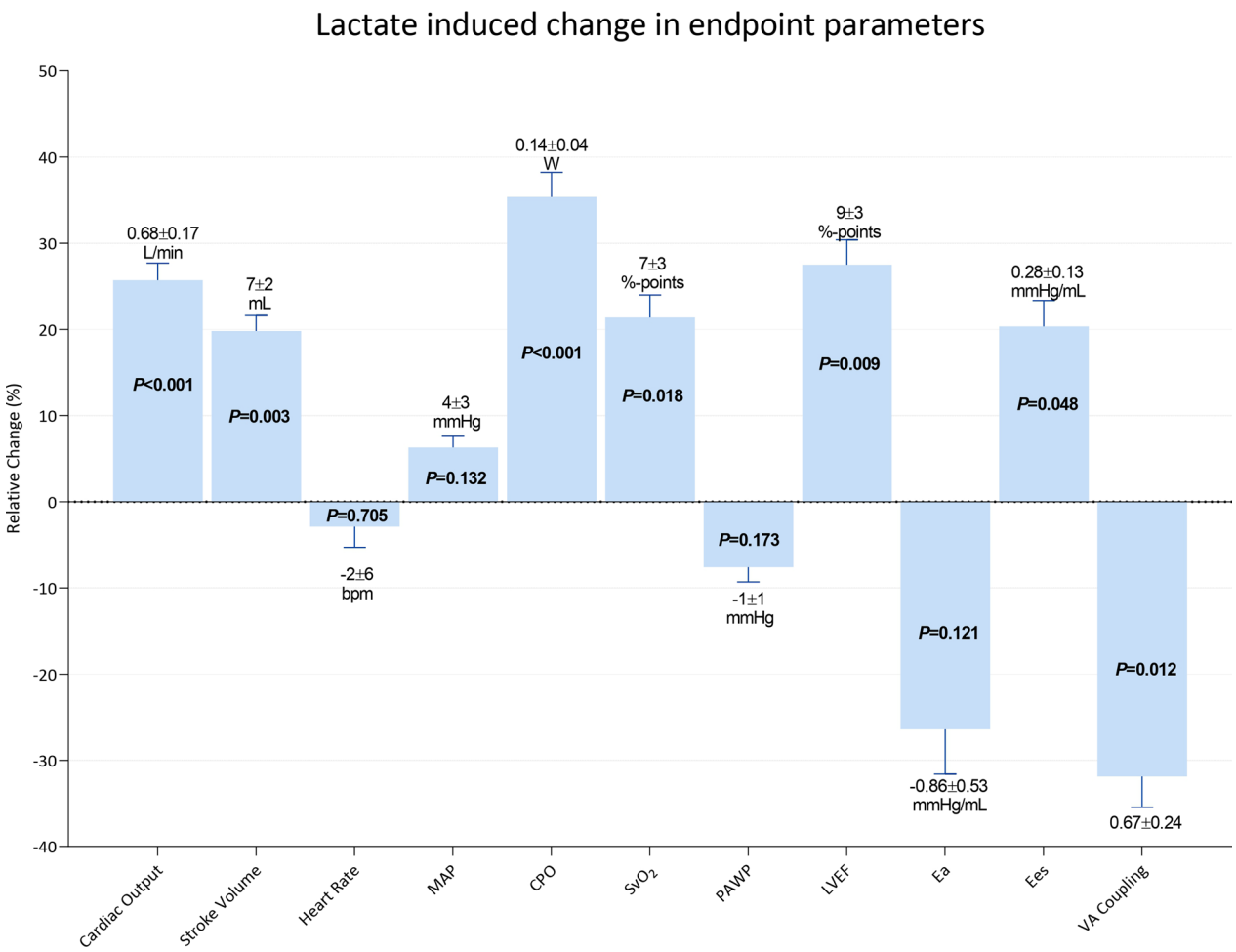


Fig. 3 Relative and absolute changes in hemodynamic parameters during lactate versus control. Changes in endpoint parameters during 180 min of lactate infusion versus control compared with baseline. Bars represent mean relative change during lactate infusion compared with control infusion and error bars indicate SEM. Corresponding mean absolute changes ± SEM are listed above or below each bar. *P*-values are stated on all results. *CO* Cardiac output, *CPO* Cardiac power output, *Ea* Arterial elastance, *Ees* End-systolic elastance, *LVEF* Left ventricular ejection fraction, *MAP* Mean arterial blood pressure, *PAWP* Pulmonary artery wedge pressure, SvO_2 Mixed venous oxygen saturation, *VA Coupling* Ventriculo-arterial coupling (Ea/Ees)

mechano-energetic function as evidenced by enhanced cardiac mechanical efficiency. These favorable cardiovascular effects were accompanied by increased transcardiac lactate gradient and improved mitochondrial function, while no adverse increases in surrogate parameters of myocardial oxygen consumption (PVA, CW, and CPP) were observed.

Lactate infusion enhanced the hemodynamic status in CS

CS is characterized by impaired contractile function with reduced CO and organ perfusion [1, 2]. The resulting drop in MAP triggers vasoconstriction to preserve perfusion, but the increased afterload exceeds the capacity of the heart, causing VA decoupling. This intensifies ventricular strain, worsens ischemia, and disrupts cardiac metabolism, leading to progressive hemodynamic decline and circulatory collapse. Hence, the primary treatment goal in CS is to reestablish organ perfusion by restoring systemic blood pressure and CO [2, 3]. A previous study demonstrated that treatment with lactate infusion in patients with acute heart failure and reduced LVEF led to an increase in CO [18]. Similar hemodynamic improvements have been observed in patients with non-ischemia-related CS [19].

The findings of the present study extend the understanding of therapeutic exogenous lactate infusion to the domain of ischemic CS and provide insights into the cardiovascular effects of lactate treatment in this setting. Foremost, the primary endpoint, CO, increased by 26% during lactate infusion compared with control. This

Table 3 Biochemical parameters during lactate and control infusions

Variable	Lactate		Control		Linear mixed model	
	Shock (n=10)	After 180 minutes	Shock (n=10)	After 180 minutes	Effect of lactate vs. control (95% CI)	*P*-value
Arterial blood samples						
Lactate, mmol/L	2.4±1.1	7.7±1.1‡	2.6±1.0	1.7±2.0	5.1 (4.4 to 5.8)	**<0.001**
Glucose, mmol/L	5.8±1.8	7.7±1.3‡	7.5±1.7	7.2±1.0	1.4 (0.3 to 2.4)	**0.013**
Free fatty acids, mmol/L	0.43±0.13	0.30±0.14†	0.44±0.19	0.39±0.17	– 0.08 (– 0.20 to 0.04)	0.225
Sodium, mmol/L	138±1	149±3‡	138±1	150±1‡	– 2 (– 3 to –1)	**0.038**
Potassium, mmol/L	4.1±0.4	3.4±0.3‡	4.0±0.2	4.2±0.3	– 0.5 (– 0.8 to –0.3)	**<0.001**
pH	7.45±0.04	7.58±0.04‡	7.45±0.04	7.43±0.06	0.11 (0.08 to 0.14)	**<0.001**
Bicarbonate, mmol/L	26.2±2.0	39.2±1.1‡	27.1±1.8	26.0±2.9	9.0 (7.6 to 10.4)	**<0.001**
Hemoglobin, mmol/L	6.6±0.7	6.1±0.7†	6.4±0.5	5.9±0.6‡	–0.1 (–0.5 to 0.2)	0.390
Perfusion and oxygenation indices						
Regional P(v-a)CO_2, kPa						
Cardiac	1.93(1.51;2.35)	1.19(0.92;1.46)†	2.02(1.85;2.35)	1.52(1.41;1.64)	– 0.28 (– 0.47 to –0.09)	**0.012**
Renal	1.01(0.22;1.65)	0.31(0.17;0.76)	0.94(0.24;2.19)	1.21(0.28;1.79)	– 0.16 (– 0.75 to 0.42)	0.596
SO_2, %						
Arterial	96.5±2.8	98.3±1.3	97.9±1.4	97.2±1.5	1.7 (0.04 to 3.4)	0.061
CS	22.4±9.7	37.5±10.5†	26.6±9.3	36.7±10.3†	8.9 (– 0.9 to 16.8)	0.07
Renal	54.8±19.3	63.4±20.5	45.9±24.0	44.9±16.3	4.9 (– 7.3 to 17.1)	0.406
Arterio-venous differences across organs						
Lactate, mmol/L						
Cardiac	–0.1±0.4	0.8±0.5†	– 0.2±0.4	– 0.1±0.3	1.1 (0.6 to 1.4)	**<0.001**
Renal	0.3(0.1;0.6)	0.6(0.4;0.7)	0.3(0.1;0.5)	0.1(– 0.1;0.3)	0.2 (– 0.5 to 1.0)	0.584
Glucose, mmol/L						
Cardiac	0.4±0.8	0.8±1.1	1.1±0.7	0.5±0.7	0.6 (– 0.1 to 1.4)	0.123
Renal	0.0±1.0	0.1±0.8	0.8±1.0	0.3±0.8	– 0.4 (– 2.3 to 1.5)	0.684
Free fatty acids, mmol/L						
Cardiac	– 0.02±0.19	– 0.03±0.11	– 0.08±0.23	0.01±0.10	– 0.13 (– 0.26 to 0.00)	0.075
Renal	0.06±0.17	– 0.02±0.27	– 0.08±0.35	– 0.09±0.35	– 0.10 (– 0.37 to 0.17)	0.510
Oxygen, mL/dL						
Cardiac	6.6±1.2	5.0±1.0‡	6.2±0.9	4.8±0.9‡	– 0.6 (– 1.4 to 0.2)	0.138
Renal	3.9±1.2	2.6±0.9	4.5±2.2	4.2±1.3	– 0.7 (– 1.7 to 0.4)	0.218

Values are expressed as mean ± SD or median (interquartile range). Levels of arterial metabolites, electrolytes, acid–base parameters and hemoglobin are shown. Arterial, coronary sinus (CS), and renal vein oxygen saturations (SO_2) are shown. Veno-arterial differences regarding metabolites, oxygen, and CO_2 contents are calculated using the CS, renal vein, and arterial blood samples

Pairwise comparisons were assessed using a repeated measurements linear mixed model with time and treatment as fixed effects and each animal as random effects. **Bold** indicates $P < 0.05$ of the linear mixed model analysis

Paired t-test or Wilcoxon signed-rank test was performed comparing mean or median after 180 min of treatment with shock levels in each treatment group. ‡ Indicates $P < 0.001$, † indicates $P < 0.01$ and * indicates $P < 0.05$

95% *CI* 95% confidence interval

increase was predominantly mediated through increased SV while MAP was maintained stable. In this regard, the contractility measures Ees and dP/dt(max) were higher compared with control and we observed an increase in CPO which is associated with improved prognosis in patients with CS [23]. Thus, VA coupling and LVEF also improved, resulting in reduced LVESV. Other LV preload and afterload metrics did not differ significantly between the treatments. Notably, the observed lactate-induced CO increase is comparable to supportive doses of common pharmacologic agents such as milrinone, dobutamine, and levosimendan in patients with severe heart failure and CS [29–31]. However, in addition to inotropic effects, these agents carry potential deleterious side effects such as increased chronotropy with associated risk of arrhythmias and increased myocardial oxygen consumption [32]. In this context, the CO increase during lactate infusion was achieved without significantly

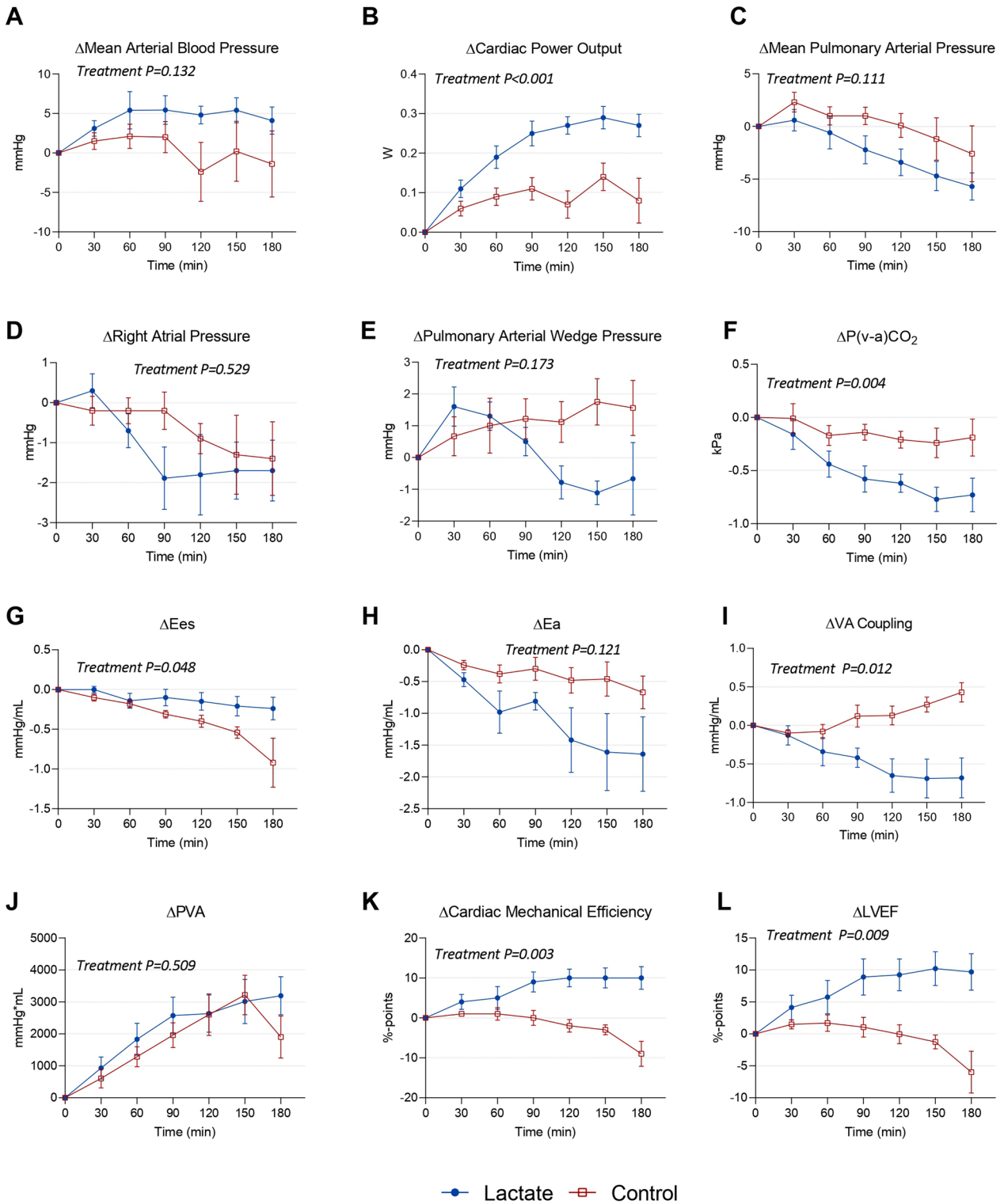


Fig. 4 Temporal evolution in hemodynamic parameters during lactate and control. Data are shown as mean ± SEM. Temporal evolution in **A** mean arterial blood pressure, **B** cardiac power output, **C** mean pulmonary arterial pressure, **D** right atrial pressure, **E** pulmonary arterial wedge pressure, **F** veno-arterial carbon dioxide difference, **G** end-systolic elastance, **H** arterial elastance, **I** ventriculo-arterial coupling, **J** pressure-volume area, **K** cardiac mechanical efficiency, and **L** LV ejection fraction from baseline and until 180 min after treatment initiation. *P*-values are derived from the pairwise comparisons assessed using a repeated measurements linear mixed model with time and treatment as fixed effects and each animal as random effects. *Ea* arterial elastance, *Ees* end-systolic elastance, *LVEF* left ventricular ejection fraction, *PVA* Pressure–volume area, *P(V-A)CO*$_2$ veno-arterial carbon dioxide difference, *VA Coupling* Ventriculo-arterial coupling (Ea/Ees)

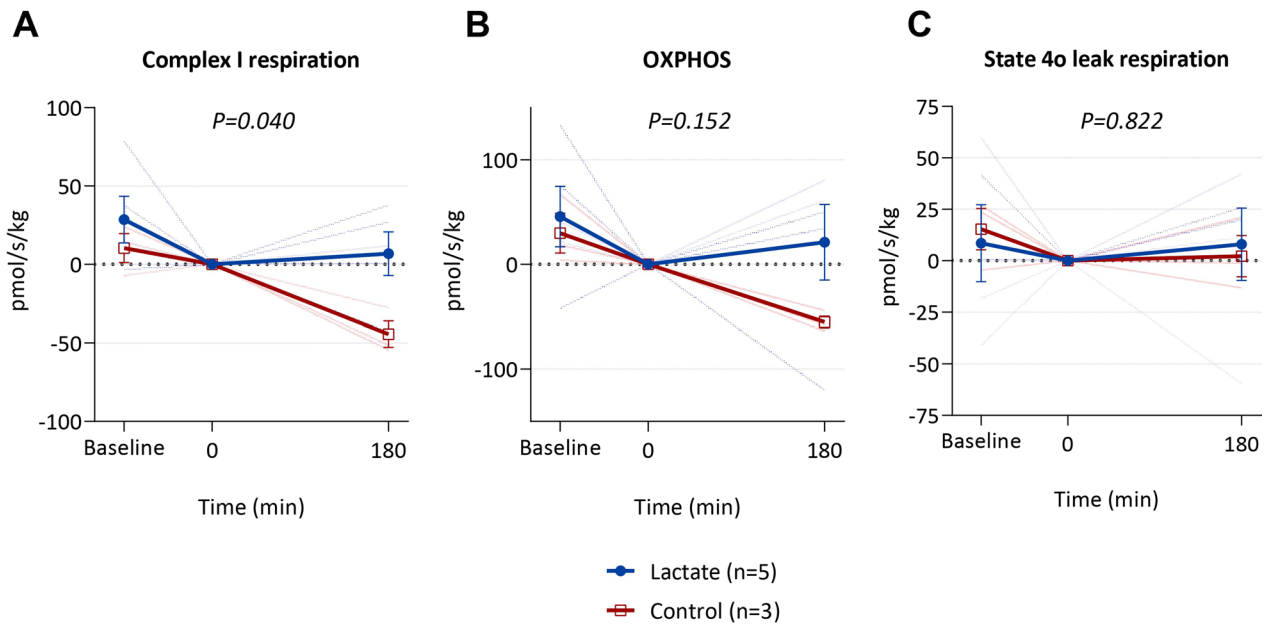


Fig. 5 Temporal evolution in left ventricular myocardial mitochondrial function parameters **A** complex I respiration, **B** OXPHOS, and **C** state 4o leak respiration during lactate versus control. Difference in mitochondrial parameters in healthy state (baseline) and after 180 min of treatment compared with cardiogenic shock baseline (Time = 0). Data are shown as mean ± SEM. Each replicate is shown. *P*-values are derived from an unpaired t-test on the change from time 0 to time 180. *OXPHOS* oxidative phosphorylation

affecting HR compared with control, and we observed no excess risk of arrhythmias compared with control.

A hallmark of CS is the inability of the heart to accommodate metabolic and oxygen demands of the organs [2]. Hence, it is intriguing that parameters such as SvO_2 and $P(v\text{-}a)CO_2$ improved during lactate infusion, as these changes indicate enhanced tissue oxygen delivery and improved microcirculatory function [33–35]. Additionally, lactate infusion was associated with increased diuresis which may also indicate improved end-organ perfusion.

In healthy pigs, lactate infusion reduces SVR and afterload, with an increase in CO driven primarily by elevated HR without significantly affecting contractility [11]. In contrast, in the present study, lactate infusion enhanced contractility (higher Ees) and SV compared with control. These pathophysiology-dependent effects suggest that in the setting of ischemic CS where compensatory sympathoadrenergic mechanism prevail [36], the inotropic benefits of lactate become more prominent. Also, in our previous study, lactate levels were elevated to a greater extent than in the current investigation, which may have contributed to the differing effects.

Metabolic aspects of lactate infusion in CS

The heart can metabolize various substrates, including FFAs, glucose, ketone bodies, and lactate, with a preference for FFAs under normal conditions [37]. Lactate enters cells insulin-independently, unlike glucose. Notably, increased lactate oxidation has been associated with increased cardiac mechanical efficiency in experimental models of hemorrhagic shock [38] and in patients with congestive heart failure [20]. Thus, lactate has been proposed as an alternative myocardial substrate during cardiac disarray. We demonstrated an increased A-V gradient of lactate across the heart, while the FFA gradient showed a declining trend, pointing to an increased myocardial uptake of lactate, decreased FFA uptake, and unchanged glucose uptake. Notably, lactate infusion led to preserved myocardial complex I mitochondrial respiratory function. As complex I is particularly susceptible to ischemic injury [39], our findings point to a potential mitochondrial-protective effect of lactate infusion during ischemic conditions. As the mitochondria were analyzed ex vivo in absence of substrates like lactate and FFAs these results points to a lasting preservation of mitochondrial function of lactate rather than a transient, substrate driven augmentation.

Several mechanisms may underlie the observed cardiometabolic effects. First, lactate may serve as a readily oxidizable substrate for the failing heart with a greater ATP per oxygen yield than FFAs [40, 41]. While lactate can be metabolized through the pyruvate pathway, lactate per se can also be oxidized [42, 43]. Second, lactate may stimulate the electron transport chain activating oxidative phosphorylation independently of its conversion

to pyruvate and thereby improve hemodynamic function [44]. Third, other properties of lactate include alteration of gene expression through histone lactylation [45, 46], and finally, lactate may improve cardiovascular effects independently of energy production through pleiotropic effects such as HCA_1-receptor activation [47, 48]. Future investigations comparing lactate infusions with pyruvate infusions, along with real-time metabolic flux assessments, would be valuable in further delineating their respective contributions to myocardial function in CS.

Cardiac mechanical efficiency was also enhanced during lactate infusion, demonstrating a more favorable balance between stroke work and the total cardiac energy demand [11, 20, 49]. Also, a trend toward elevated coronary sinus SO_2 was noted, albeit with a similar trending increase in arterial SO_2, leaving the transcardiac SO_2 difference unchanged between treatments. Correspondingly, PVA, CW, and RPP, which are indicators of myocardial oxygen consumption [50, 51] did not differ between lactate and control treatment, reflecting that the increase in cardiovascular performance observed with lactate infusion was not accompanied by excess myocardial oxygen consumption.

Ultimately, these findings suggest that lactate infusion enhances mechanical efficiency and contractility without imposing additional metabolic demand on the heart. It remains to be determined whether the mitochondrial effects of lactate infusion provide a direct cardioprotective mechanism through advantageous metabolic properties, or if they represent an indirect benefit to mitochondria due to improved hemodynamic conditions (e.g. improved VA coupling and mechanical efficiency) which leads to adequate output with minimal energy expenditure.

Clinical perspectives

As expected, endogenous production of lactate increased during induction of CS. While lactate traditionally has been seen as a marker of disease severity, studies suggest that lactate per se is protective rather than harmful. Indeed, in experimental shock, systemic lactate deprivation is associated with compromised myocardial function and increased mortality [38, 52]. The present study demonstrated significant beneficial hemodynamic effects of exogenous lactate administration in CS, which appeared to plateau at plasma lactate concentrations above 5 mmol/L (Fig. 2A–B). This finding points to that increasing lactate levels beyond this threshold, which may occur in the most profound cases of CS [53], may not yield additional hemodynamic benefits. However, the most severe cases of CS are often accompanied by metabolic acidosis. In this context, the alkalizing effect of exogenous lactate infusion, as observed in the present study, could represent a relevant clinical effect. This, however, must be explored in future studies. Also notably, the concomitant administration of dobutamine on top of lactate infusion resulted in further hemodynamic improvements, indicating that lactate infusion could potentially be incorporated into contemporary management strategies for CS.

Limitations

First, extrapolation of findings in experimental studies requires caution. To enhance translatability and clinical relevance, we chose human-sized pigs as experimental animals, as they have close cardiothoracic anatomical and physiological similarities with humans. However, porcine and human metabolism cannot be interchanged which may limit the generalizability from pigs to humans. Still, similar hemodynamics effects of lactate infusions have been found in patients with acute heart failure and non-ischemic CS [18, 19]. Also, CS induced by coronary occlusion through microsphere injections may differ from the disease resulting from atherosclerotic disease with plaque rupture and myocardial infarction or acute decompensated heart failure. Nevertheless, the model is well validated, and the hemodynamic alterations observed were vastly similar to patients with ischemic CS [22].

The current study utilized an equimolar, euvolemic saline infusion as a control with the same tonicity as the lactate infusion. Hence, the observed between treatment hemodynamic effects are unlikely to be explained by the tonicity of the lactate infusion. Still, hypertonic fluids can cause hemodynamic alterations. Indeed, hypertonic fluids reduce SVR and elevate CO following cardiac surgery [54]. Importantly, dobutamine was administered as a positive control, to rule out any persistent detrimental effect of the control solution. These data showed a significant cardiovascular response and did not indicate any adverse cardiac effects from the hypertonic control solution. Also, no effect was seen on preload parameters such as RAP and LVEDV between the treatments.

Lactate infusion resulted in metabolic alkalosis which is also known to have hemodynamic impacts [55]. Notably, our previous study demonstrated that CO increased during lactate infusion in healthy pigs independently from pH and bicarbonate levels [11]. Furthermore, hemodynamic improvements are superior during lactate treatment when comparing lactate with bicarbonate [14, 15]. Thus, it appears unlikely that the hemodynamic and cardiometabolic findings in the present study could be explained by alkalosis. In fact, alkalosis may cause vasoconstriction potentially blunting the potential hemodynamic benefit from lactate infusion [56]. Nevertheless, as lactate was not compared to an alkalizing control in this

study, it was not possible to distinguish between direct effects from lactate and its metabolism from effects of subsequent metabolic alkalosis as the latter follows the former.

We catheterized the coronary sinus and renal vein to measure metabolite and gas gradients across organs, though without direct assessment of coronary or renal flow. Consequently, observed differences may reflect differences in myocardial perfusion. In addition, gradients across the heart do not take myocardial production of lactate from e.g. glycogen into account [57].

Finally, while permeabilized fiber techniques are a well-validated approach for assessing mitochondrial respiratory capacity, they do not entirely replicate the natural physiological setting. This introduces some uncertainty regarding the direct application of these findings at the whole organ level. Furthermore, the small sample size raises the possibility of regression toward the mean, where extreme values might appear closer to the average with repeated measures, potentially obscuring true variability or change [58]. Therefore, these data should be interpreted with caution, acknowledging these limitations. Nevertheless, the findings appear to demonstrate preserved mitochondrial function during lactate infusion.

Conclusion

Lactate infusion enhanced cardiac output and peripheral perfusion in ischemic CS, primarily through increased stroke volume, improved contractility, and enhanced ventriculo-arterial coupling, without affecting heart rate or systemic blood pressure. These effects were accompanied by better mechano-energetic and mitochondrial function, suggesting lactate as a potential therapeutic approach for CS.

Clinical perspectives

Clinical competencies

Medical knowledge: For the first time, this study utilized excessive hemodynamic monitoring with state-of-the-art techniques including right-, and left heart catheterization for hemodynamic assessment, mitochondrial analysis, and across-organ catheterization for blood sampling. The study highly expands the knowledge regarding hemodynamic effects of lactate infusion in critical care disease, highlighting that lactate infusion in ischemic cardiogenic shock can improve cardiac output, contractility, and ventriculo-arterial coupling, while enhancing peripheral perfusion without increasing markers myocardial oxygen demand.

Translational outlook

This experimental work suggests that lactate infusion can enhance cardiac function and metabolic efficiency in ischemic cardiogenic shock. It is the most rigorously designed study in the field with state-of-the-art implementation of hemodynamic and cardiovascular monitoring and measurement. However, before implementation in clinical practice, several translational steps remain. Future research should investigate patient selection, optimal dosing, and safety parameters of lactate infusion, followed by rigorously designed clinical trials. Additionally, integrating lactate infusion into existing treatment pathways and ensuring broad practitioner acceptance will be crucial. By streamlining these steps, from preclinical validation to clinical application, this therapy could ultimately improve patient outcomes and potentially reshape the management of ischemic cardiogenic shock.

Abbreviations

A-V	Arterio-venous
CI	Confidence interval
CO	Cardiac output
CPO	Cardiac power output
CPP	Coronary perfusion pressure
CS	Cardiogenic shock
CW	Cardiac work
dP/dt(max)	Maximum rate of left ventricular pressure rise
dP/dt(min)	Minimum rate of left ventricular pressure decay
Ea	Arterial elastance
Ees	End-systolic elastance
ESPVR	End-systolic pressure–volume relationship
FFA	Free fatty acid
HR	Heart rate
IQR	Interquartile range
LV	Left ventricle/left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESP	Left ventricular end-systolic pressure
LVESV	Left ventricular end-systolic volume
MAP	Mean arterial pressure
mPAP	Mean pulmonary artery pressure
PaPi	Pulmonary artery pulsatility index
PAWP	Pulmonary artery wedge pressure
$P(v\text{-}a)CO_2$	Venous-to-arterial CO_2 tension difference
PVR	Pulmonary vascular resistance
PVA	Pressure–volume area
RAP	Right atrial pressure
RPP	Rate-pressure-product
SD	Standard deviation
SO_2	Oxygen saturation
SV	Stroke volume
SVR	Systemic vascular resistance
SW	Stroke work
VA Coupling	Ventriculo-Arterial Coupling

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05346-2.

Additional file 1

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Author contributions
OKH was the first author and carried out the experiments underlying the presented data, performed the data analysis, wrote the primary draft of the manuscript and aquisited funding. MSE, AML and HG helped carrying out the experiments underlying the presented data, and contributed writing the final manuscript. NM was involved in the design of the experiments, supervised the project and contributed writing the final manuscript. JEM, OKLH, HBR developed the animal model and provided expert experimental advise and supervised the project and contributed writing the final manuscript. HW and RN provided expert supervision and were involved in the design of the experiments and contributed writing the final manuscript. NG and KBH are contributing lead investigators and were involved in funding aquisition, design, data analysis, primary draft and final manuscript.

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Availability of data and materials
The data analysed in the current study is available from the corresponding author upon reasonable request.

Declarations

Ethics Approval and consent to participate
The study was conducted after obtaining the necessary authorization from the Danish National Animal Experiment Inspectorate. (*Hemodynamic Optimization with Carbonates, Permit no: 2023-15-0201-01466, issued on 19/06-2023*). The treatment administered and ethical oversight concerning the animals strictly adhered to established animal welfare protocols and regulatory standards mandated by both Danish and European legislation. The methodologies employed and the handling of animals conformed to the guidelines outlined in the EU Directive 2010/63/EU pertaining to animal experimentation.

Consent for publication
Not applicable.

Competing interests
Roni Nielsen has collaboration with the pharceutical companies Imbria, Medtrace, Resother as an investigation and has received lectural fee from Astrazeneca. Roni Nielsen is a patentholderof 20205938.2 A Lactate/Ketone Body ester, 5-11-2020. Henrik Wiggers has been the principal or a sub-investigator in studies involving the following pharmaceutical companies: MSD, Bayer, Daiichi-Sankyo, Novartis, Novo Nordisk, Sanofi-Aventis, and Pfizer.

Tweet
In this experimental study in ischemic cardiogenic shock in human-sized pigs by @OHorsdal et al, infusion with #lactate increased cardiac output due to increased stroke volume. Contractility was increased and mitochondrial function was enhanced during lactate infusion.

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