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Cardiovascular effects of lactate in healthy adults

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Abstract

Background Low-volume hypertonic solutions, such as half-molar lactate (LAC), may be a potential treatment used for fluid resuscitation. This study aimed to evaluate the underlying cardiovascular effects and mechanisms of LAC infusion compared to sodium-matched hypertonic sodium chloride (SAL).

Methods Eight healthy male participants were randomized in a controlled, single-blinded, crossover study. Each participant received a four-hour infusion of LAC and SAL in a randomized order. Assessor-blinded echocardiography and blood samples were performed. The primary endpoint was cardiac output (CO) measured by echocardiography.

Results During LAC infusion, circulating lactate levels increased by 1.9 mmol/L (95% CI 1.8–2.0 mmol/L, $P<0.001$) compared with SAL. CO increased by 1.0 L/min (95% CI 0.5–1.4 L/min, $P<0.001$), driven primarily by a significant increase in stroke volume of 11 mL (95% CI 4–17 mL, $P=0.002$), with no significant change in heart rate. Additionally, left ventricular ejection fraction improved by 5 percentage points ($P<0.001$) and global longitudinal strain by 1.5 percentage points ($P<0.001$). Preload indicators were elevated during SAL infusion compared with LAC infusion. Concomitantly, afterload parameters, including systemic vascular resistance and effective arterial elastance, were significantly decreased with LAC infusion compared with SAL, while mean arterial pressure remained similar. Indicators of contractility improved during LAC infusion.

Conclusions In healthy participants, LAC infusion enhanced cardiac function, evidenced by increases in CO, stroke volume, and left ventricular ejection fraction compared with SAL. Indicators of contractility improved, afterload decreased, and preload remained stable. Therefore, LAC infusion may be an advantageous resuscitation fluid, particularly in patients with cardiac dysfunction.

Clinical trial registrations https://clinicaltrials.gov/ct2/show/NCT04710875. Registered 1 December 2020.

Keywords Lactate, Cardiac output, Left ventricular ejection fraction, Preload, Afterload, Echocardiography

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Introduction

Hospitalized patients with low blood pressure often receive large amounts of intravenous fluids to enhance cardiac output (CO) and improve end-organ perfusion [1]. It remains a clinical challenge to balance hypo- and hypervolemia which both can increase mortality and no consensus exists on the optimal type of intravenous fluid for resuscitation [2, 3]. To minimize fluid overload, the concept of small-volume resuscitation with hypertonic saline has been employed. Low volumes of hypertonic saline can improve CO, vascular tone, and microcirculation [4–6] but may also induce hyperchloremia and metabolic acidosis, and thereby renal vasoconstriction and lower glomerular filtration rate [7]. Therefore, the use of other hypertonic crystalloid solutions for fluid resuscitation offers potential advantages, as improved hemodynamic effects are achieved without co-administration of chloride. In this context, hyperosmolar sodium-lactate has emerged as a promising infusion therapy. Studies have demonstrated enhanced end-organ perfusion and CO in acute heart failure and after coronary artery bypass grafting [5, 8, 9]. Despite these promising effects of hyperosmolar sodium-lactate, the physiological basis of the hemodynamic and cardiac effects have not been thoroughly investigated. In the present study, we aimed to investigate the hemodynamic effects and underlying mechanisms of a four-hour half-molar sodium lactate (LAC) infusion compared with hypertonic sodium chloride (SAL) in healthy participants.

Methods

Study design

Eight healthy participants were enrolled in a randomized, controlled, single-blind, crossover study (Fig. 1). This study served as a pre-planned sub-study of a clinical trial aiming to assess the metabolic effects of LAC infusion, with detailed methods and results previously published [10]. Each participant received a four-hour infusion of LAC and SAL in random order on two separate study days, with a minimum interval of 14 days between the sessions. Apart from the interventions, both study days followed identical protocols.

Participants were instructed to avoid strenuous physical activity, alcohol, and maintain a regular diet for 48 h before each study day. They also fasted for 10 h prior to the study and arrived at the research lab by bus, car, or taxi to minimize physical exertion. Upon arrival, participants rested in bed throughout the study day. A peripheral venous catheter was inserted into the cubital vein for blood sampling. All participants were positioned in the

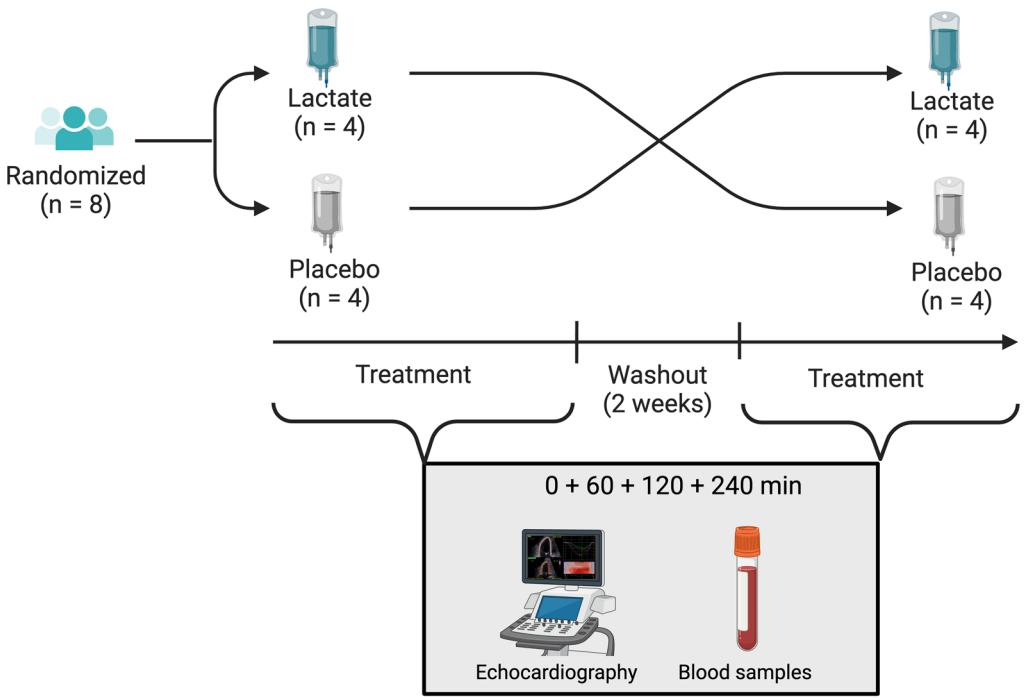

Fig. 1 Study design. A randomized, double-blind, controlled cross-over trial in eight participants investigated at two study visits separated by ≥ 14 days washout period. At the first visit, participants were randomized to receive an intravenous infusion of either weight-adjusted half-molar sodium lactate (LAC) infusion or hypertonic sodium chloride (SAL). At the second visit, participants received the opposite treatment compared with the first visit. Serial echocardiographic evaluation and blood samples were collected before the infusion and at 60, 120, and 240 min during infusion

supine position for a minimum of 10 min prior to each measurement. Echocardiography and blood samples were collected at baseline and 60, 120, and 240 min during both LAC and SAL infusions. The main study utilized a hyperinsulinemic-euglycemic clamp (HEC) to study the insulin sensitivity during LAC compared with SAL; these results have been reported [10]. The HEC was initiated at 180 min during each treatment [10]. Thus, measurements at 240 min in the present study were performed during the HEC. Specifically, 0.6 mU/kg/min insulin (Actrapid, Novo Nordisk, Denmark) was continuously infused in parallel with 20% glucose which was titrated to maintain a constant glucose level of 5 mmol/L. Fluid intake and urine output were recorded throughout the study visits.

The study was conducted at Aarhus University Hospital, Aarhus, Denmark, between March and June 2021, and was approved by the Ethics Committee of the Central Denmark Region. The study adhered to the CONSORT reporting guidelines.

Participants

Eight healthy participants were included in the study. The inclusion criteria were male sex, age ≥ 18 years, and body mass index between 18 and 30 kg/m^2. Exclusion criteria included the daily use of medication, any abnormalities in routine screening blood tests, or the presence of acute or chronic diseases, including known heart disease.

Interventions

The LAC infusion consisted of a racemic sodium lactate mixture (Monico, S.P.A, Italy) containing 45 g of lactate per liter, equivalent to 0.5 mol/L (Supplementary file). During the initial 30 min, a bolus was administered at a rate of 50 µmol/kg/minute, followed by a continuous infusion of 25 µmol/kg /minute for the remaining 210 min. Dosing was based on actual body weight. The control was a sodium-matched hypertonic sodium chloride solution (SAL), infused at the same volumes as the LAC infusion.

Endpoints

The pre-planned primary endpoint was mean change in CO during the four-hour LAC infusion and SAL infusion. The secondary endpoints included SV, LVEF, global longitudinal strain (GLS), effective arterial elastance (Ea), and systemic vascular resistance (SVR).

Transthoracic echocardiography

Blood pressure (BP) and heart rate (HR) were measured non-invasively. All transthoracic echocardiographic data were acquired by an experienced echocardiographer using a 3.5-MHz transducer on a GE Vivid E95 system (GE Healthcare, USA) and analyzed with EchoPAC software (version 206, GE-Vingmed Ultrasound, Norway). The analysis was performed by another assessor who was blinded to the order of randomization. All parameters were calculated as the mean of three cardiac cycles. CO was estimated as the LV outflow tract (LVOT) area multiplied by the LVOT velocity time integral and HR. The LVOT area was derived from the LVOT diameter in the parasternal long-axis view during the first exam. The LVOT velocity time integral was measured using pulsed wave Doppler from the LVOT in the apical five-chamber view. Right atrial pressure was estimated based on inferior vena cava diameter and the respiratory variability [11]. Mean arterial blood pressure (MAP), systemic vascular resistance (SVR = [MAP-right atrial pressure]/CO), and effective arterial elastance (Ea = 0.9 × [systolic BP]/SV) were calculated [12]. End-systolic elastance (Ees) was estimated using the modified single-beat method [13]. Also, preload-independent measures of LV contractility were estimated, including LV stroke work normalized to LVEDV (LVSW/EDV) and preload recruitable stroke work (PRSW) [14, 15]. Systolic pulmonary artery pressure was estimated from the peak systolic velocity of tricuspid regurgitation using continuous-wave Doppler and applying the modified Bernoulli equation, with the addition of the estimated right atrial pressure. [16]

LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes and LVEF were assessed using the Simpson biplane method from apical views, and GLS was obtained from the three apical views: four-chamber, two-chamber, and apical long-axis projections [17]. LV myocardial work parameters, including global wasted and constructive work, as well as global work efficiency and index, were calculated from the three apical views as previously described [18]. Early (E) and late (A) diastolic mitral inflow velocities were measured, and tissue Doppler imaging from the apical view was used to obtain septal and lateral early diastolic mitral plane tissue velocity (e') and peak systolic velocity (s'). Left atrial volume was calculated using the Simpson biplane method, and left atrial (LA) reservoir, conduit, and contractile strain was assessed from the two apical views (four-chamber and two-chamber projections) [19]. Right ventricular (RV) free wall longitudinal strain, tricuspid annular peak systolic velocity (RV S'), and tricuspid annular plane systolic excursion (TAPSE) were measured from an RV-focused apical view. [20]

Blood samples

Venous pH, potassium, sodium, chloride, glucose, hematocrit, bicarbonate, pCO_2, and lactate were analyzed immediately following venous blood gas sampling (ABL90 FLEX PLUS, Radiometer, Denmark).

Statistical methods

Participant characteristics are presented as medians with interquartile ranges. A linear mixed model was employed to compare the effects of LAC infusion with SAL infusion. Treatment and treatment-by-time interaction were defined as fixed effects, while participants were treated as random effects. P-values were derived from least-squares means analysis of the linear mixed models. Residuals were assessed for normality and homoscedasticity, with log-transformations applied if necessary. The effect size of LAC compared to SAL is reported as the pairwise mean difference with a 95% confidence interval. Statistical significance was defined as $P<0.05$. All data analyses, tables, and figures were generated using R software (version 2022.02.3, Build 492; R Core Team (2022); R Foundation for Statistical Computing, Vienna, Austria). The first authors had full access to all study data and are responsible for its integrity and analysis. Data supporting the study findings are available from the corresponding author upon reasonable request.

Results

Eight participants completed the study. The median age was 26 years (interquartile range 23–29 years), the median body weight was 78 kg (interquartile range 72–88 kg), and the median body mass index was 23.0 kg/m^2 (interquartile range 20.6–26.7 kg/m^2). All participants were white.

Hemodynamic effects of LAC infusion

LAC infusion increased circulating lactate from 0.9 ± 0.3 to 2.5 ± 0.8 mmol/L during the four-hour treatment period (SAL-adjusted difference: 1.9 mmol/L, 95% CI 1.8–2.0 mmol/L, $P<0.001$; Table 1 and Fig. 2), as previously reported [10]. This was associated with a significant increase in CO, with a SAL-adjusted difference of 1.0 L/min (95% CI 0.5–1.4 L/min, $P<0.001$). The increase in CO was largely driven by an increased SV (SAL-adjusted difference: 11 mL, 95% CI 4–17 mL, $P=0.002$), while HR did not differ significantly between treatments. MAP remained similar between the treatments. The CO and SV responses to the HEC were more pronounced during SAL infusion compared with LAC (Fig. 2).

Preload parameters were generally elevated during SAL infusion compared with LAC. LA volume was significantly higher during SAL infusion and a similar trend was apparent for LVEDV (Table 2 and Fig. 3). This corroborated with increasing E/e´ during SAL infusion, with significantly higher levels at 240 min. Furthermore, systolic BP and estimated sPAP were significantly elevated during treatment with SAL compared with LAC. Meanwhile, the afterload parameters SVR and Ea were reduced during LAC treatment compared with SAL. Finally, treatment with LAC significantly increased the contractility measures LVSW/EDV ($P=0.005$) and PRSW ($P=0.031$) compared with SAL, while Ees remained similar between treatments ($P=0.234$). Overall fluid intake was similar during both treatments (Table 3). Also, there was no between-treatment difference in urine output.

Table 1 Hemodynamic parameters

	LAC		SAL		Difference (95% CI)	*P* value
	Baseline	After treatment	Baseline	After treatment		
Lactate, mmol/L	0.8 ± 0.3	2.5 ± 0.8	0.9 ± 0.3	0.9 ± 0.3	1.9 (1.8, 2.0)	**< 0.001**
Cardiac output, L/min	4.8 ± 0.7	6.5 ± 1.0	5.2 ± 1.4	5.9 ± 1.5	1.0 (0.5, 1.4)	**< 0.001**
Stroke volume, mL	82 ± 16	100 ± 18	93 ± 21	98 ± 20	11 (4, 17)	**0.002**
Heart rate, min^{-1}	59 ± 9	66 ± 7	56 ± 8	61 ± 8	3 (−1, 6)	0.15
Mean arterial pressure, mmHg	91 ± 8	88 ± 5	86 ± 4	89 ± 8	−0.3 (−3.4, 2.8)	0.84
Systolic blood pressure, mmHg	127 ± 9	127 ± 7	122 ± 10	127 ± 12	−5 (−9, −1)	**0.023**
Diastolic blood pressure, mmHg	72 ± 8	69 ± 6	67 ± 4	70 ± 8	−4 (−8, 1)	0.11
sPAP, mmHg	22.7 ± 3.7	19.3 ± 6.0	16.8 ± 7.5	21.1 ± 4.7	−4.8 (−9.6, 0.0)	**0.049**
LVSW/EDV, g/mL	0.64 ± 0.13	0.85 ± 0.29	0.71 ± 0.28	0.73 ± 0.26	0.18 (0.06, 0.31)	**0.005**
PRSW, g/cm^2	84 ± 13	101 ± 20	89 ± 20	96 ± 19	10 (1, 19)	**0.031**
Ees, mmHg/mL	1.19 ± 0.30	1.32 ± 0.32	1.10 ± 0.23	1.15 ± 0.29	0.07 (−0.05, 0.19)	0.23
Systemic vascular resistance, WU	18.5 ± 4.4	13.2 ± 2.2	16.5 ± 4.6	15.0 ± 3.9	−3.3 (−4.9, −1.8)	**< 0.001**
Ea, mmHg/mL	1.44 ± 0.27	1.18 ± 0.22	1.24 ± 0.33	1.22 ± 0.28	−0.20 (−0.29, −0.12)	**< 0.001**

Values are mean ± SD at baseline and 4-h average for each treatment and between-treatment pairwise comparison (95% CI) and associated *P*-values from a mixed model, which incorporated repeated measurements. Ea = effective arterial elastance; LAC = half-molar sodium lactate; LVSW/EDV = left ventricular stroke work normalized to end-diastolic volume; PRSW = preload-recruitable stroke work; SAL = hypertonic sodium chloride; sPAP = systolic pulmonary arterial pressure; WU = Wood units. Bold text highlights *P* values < 0.05

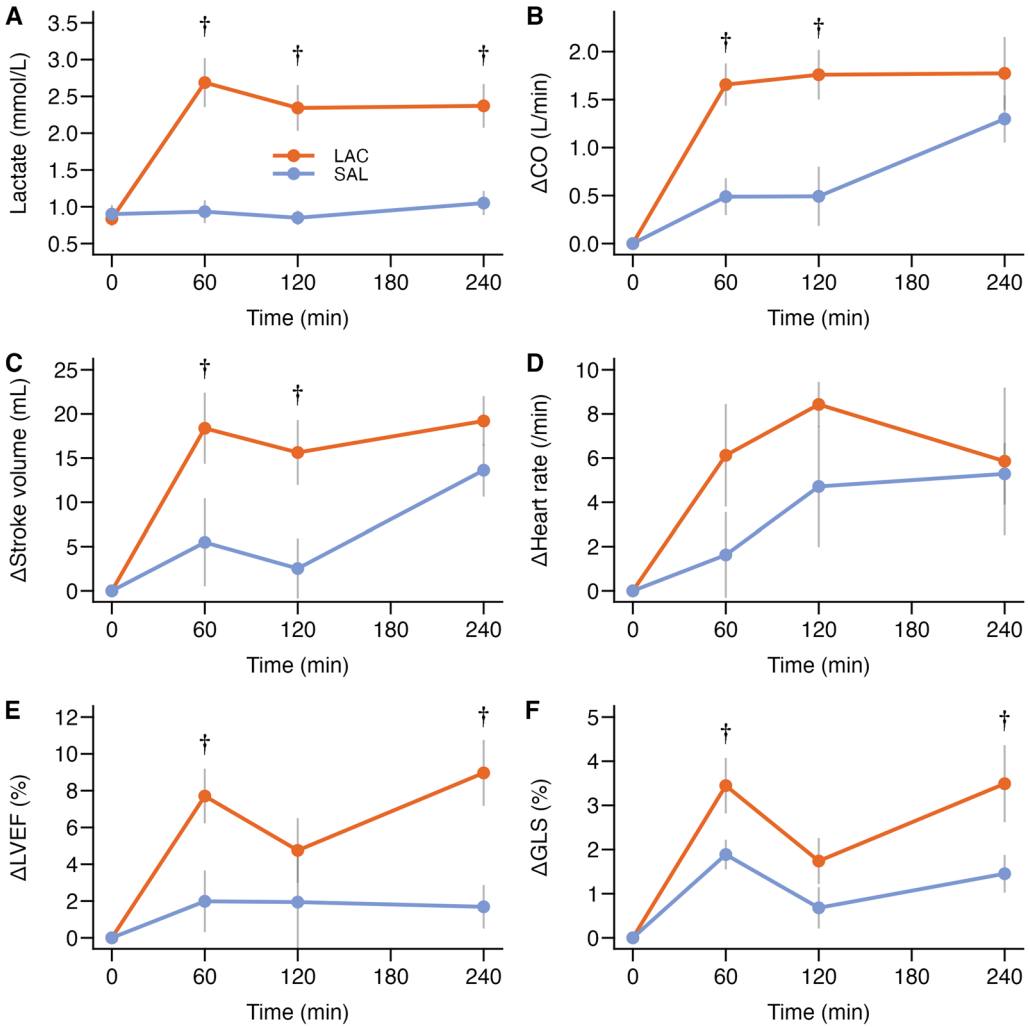

Fig. 2 Effect of each treatment on circulating lactate and hemodynamic parameters. Measurements during infusion with half-molar sodium lactate (LAC) infusion and hypertonic sodium chloride (SAL). Time = 0 indicates baseline before infusion. **A** Treatment with LAC significantly increased circulating lactate through the four-hour study period. This was associated with **B** a significant increase in cardiac output (CO) and **C** stroke volume. Meanwhile, **D** heart rate did not differ significantly. **E** Left ventricular ejection fraction (LVEF) and **F** left ventricular global longitudinal strain (LV-GLS) improved. Data are shown as mean, with bars indicating SEM. † indicates $P < 0.05$ between treatments at a given time point

Effects of LAC infusion on cardiac function

LAC infusion increased LVEF by 5 percentage points (95% CI: 3 to 8 percentage points, $P < 0.001$) and GLS by 1.5 percentage points (95% CI 0.7–2.2 percentage points, $P < 0.001$) compared with SAL (Table 2 and Fig. 3). Thus, LVESV was reduced by 10 mL (95% CI −17 to −4 mL, $P = 0.002$). LV S'max was also increased during LAC infusion ($P = 0.002$). There was no difference in LV myocardial work parameters. In terms of diastolic function, the E/A-ratio was lower during LAC treatment compared with SAL. LA strain parameters remained similar between treatments. TAPSE was increased during LAC infusion, while RV S'max and free wall LS did not differ between treatments (Table 4).

Changes in acid–base parameters and electrolytes

Treatment with LAC increased pH and bicarbonate compared with SAL. The pCO_2 did not differ between treatments. Both treatments increased sodium levels; however, SAL treatment increased sodium levels more than LAC. SAL also caused a significant increase in chloride levels compared with LAC. Calcium and potassium levels were reduced during LAC treatment compared with SAL.

Discussion

The main finding of this study was that infusion with LAC infusion increased cardiac function compared to the sodium-matched SAL through a four-hour period.

Table 2 Echocardiographic parameters

	LAC		SAL		Difference (95% CI)	*P* value
	Baseline	After treatment	Baseline	After treatment		
Left ventricular systolic function						
LVEF, %	57 ± 5	65 ± 7	59 ± 5	61 ± 6	5 (3, 8)	**< 0.001**
LVEDV, mL	135 ± 27	126 ± 33	134 ± 36	137 ± 37	− 11 (− 22, 1)	0.07
LVESV, mL	59 ± 17	46 ± 18	56 ± 20	55 ± 20	− 10 (− 17, − 4)	**0.002**
GLS, %	18.6 ± 2.2	21.9 ± 2.0	19.8 ± 1.8	21.1 ± 2.3	1.5 (0.7, 2.2)	**< 0.001**
LV S'max, cm/s	7.4 ± 1.1	9.0 ± 1.4	7.4 ± 0.9	8.3 ± 1.3	0.7 (0.2, 1.1)	**0.002**
GWI, mmHg%	1,856 ± 219	2,083 ± 249	1,881 ± 266	2,026 ± 245	49 (− 58, 155)	0.36
GCW, mmHg%	2,257 ± 199	2,590 ± 242	2,244 ± 248	2,502 ± 287	51.6 (− 61, 164)	0.36
GWW, mmHg%	114 ± 71	98 ± 46	79 ± 29	91 ± 47	− 7.6 (− 29, 13)	0.47
GWE, %	94 ± 3	95 ± 2	96 ± 2	96 ± 2	0 (− 1, 1)	0.76
Left ventricular diastolic function						
A, cm/sec	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	0.0 (− 0.1, 0.1)	0.76
E, cm/sec	0.9 ± 0.2	1.0 ± 0.1	0.9 ± 0.2	1.0 ± 0.1	0.0 (− 0.1, 0.0)	0.60
E/A	2.2 ± 0.7	1.9 ± 0.4	2.0 ± 0.5	2.1 ± 1.2	− 0.5 (− 0.9, 0.0)	**0.038**
Lateral E/e´	4.8 ± 0.6	5.0 ± 0.7	4.9 ± 1.1	5.4 ± 0.9	− 0.4 (− 0.9, 0.1)	0.10
Left atrial function						
LA volume, mL	42 ± 12	40 ± 12	37 ± 12	48 ± 18	− 16 (− 25, − 6)	**0.003**
LA Conduit strain, %	46.1 ± 9.1	51.0 ± 6.5	43.1 ± 5.8	45.7 ± 5.6	2.0 (− 1.2, 5.2)	0.21
LA Contractile strain, %	− 37.6 ± 9.2	− 42.2 ± 9.7	− 36.0 ± 3.8	− 39.1 ± 6.2	− 1.0 (− 5.1, 3.2)	0.64
LA Reservoir strain, %	− 8.6 ± 5.1	− 8.8 ± 6.7	− 7.0 ± 4.9	− 7.3 ± 5.3	− 0.4 (− 3.5, 2.8)	0.81
Right Ventricular function						
TAPSE, mm	2.6 ± 0.4	2.9 ± 0.4	2.7 ± 0.3	2.7 ± 0.5	0.2 (0.0, 0.4)	**0.021**
RV S'max, cm/s	13.4 ± 1.7	12.6 ± 3.8	14.5 ± 1.2	15.0 ± 2.2	− 1.5 (− 4.0, 1.0)	0.23
RV free wall LS, %	26.3 ± 2.0	26.9 ± 1.9	27.9 ± 3.9	28.0 ± 3.1	0.5 (− 1.7, 2.7)	0.65

Values are mean ± SD at baseline and 4-h average for each treatment and between-treatment pairwise comparison (95% CI) and associated P-values from a mixed model, which incorporated repeated measurements. E/A = ratio of early (E) and late (A) diastolic mitral in- flow velocity; E/e´ = ratio of E and early diastolic mitral plane tissue velocity (e'); GLS = global longitudinal strain; GWW and GCW = global wasted and constructive work; GWE and GWI = global work efficiency and index; LA = left atrial; LAC = half-molar sodium lactate; LS = longitudinal strain; LVEDV and LVESV = left ventricular (LV) end-diastolic and end-systolic volume; LVEF = LV ejection fraction; S'max = systolic mitral (LV S' velocity; 9-point average) and tricuspid (RV S' velocity; 3-point average) plane peak excursion velocity; SAL = hypertonic sodium chloride; TAPSE = tricuspid annular plane systolic excursion. Bold text highlights *P*-values < 0.05

LAC improved CO by 20% (i.e., 1.0 L/min) and LVEF by 5 percentage points. A higher SV rather than HR was primarily responsible for the increase in CO. MAP remained constant while other indices of afterload were reduced, and indices of contractility were improved. LAC infusion did not increase measures of preload compared to saline. Therefore, LAC infusion provides potential beneficial hemodynamic effects beyond mere volume expansion.

Increasing circulating lactate presents a promising therapeutic option for cardiovascular distress [21]. Lactate is a metabolite that serves as a fuel source for myocardial energy production. In the healthy, resting heart, the contribution of lactate to myocardial ATP production is limited, with the main fuel source being fatty acids [22]. However, myocardial lactate oxidation can increase significantly with elevated supply [23], and lactate consumption correlates with circulating levels [24, 25]. As an oxidative fuel source, lactate infusion offers a potential means to optimize cardiac energy metabolism during cardiovascular distress [26]. This corroborates with beneficial hemodynamic effects of lactate in patients with acute decompensated heart failure and in the postoperative period after cardiac surgery [5, 9]. Additionally, lactate treatment has demonstrated beneficial cardiovascular effects in animal models of cardiovascular disarray, supporting its potential as an effective resuscitation fluid with favorable hemodynamic properties [27–31]. The cardiovascular effects of SAL and LAC infusions have been compared in healthy volunteers, where both infusions equally improved CO and LVEF by increasing preload [32]. However, hemodynamic assessments in that study were conducted after only 30 min of infusion, potentially limiting the ability to fully capture the beneficial effects of LAC infusion.

In this study, LAC infusion significantly enhanced CO and LV systolic function compared to a sodium-matched control solution. Importantly, these improvements were not attributed to increased preload, as LVEDV, LA

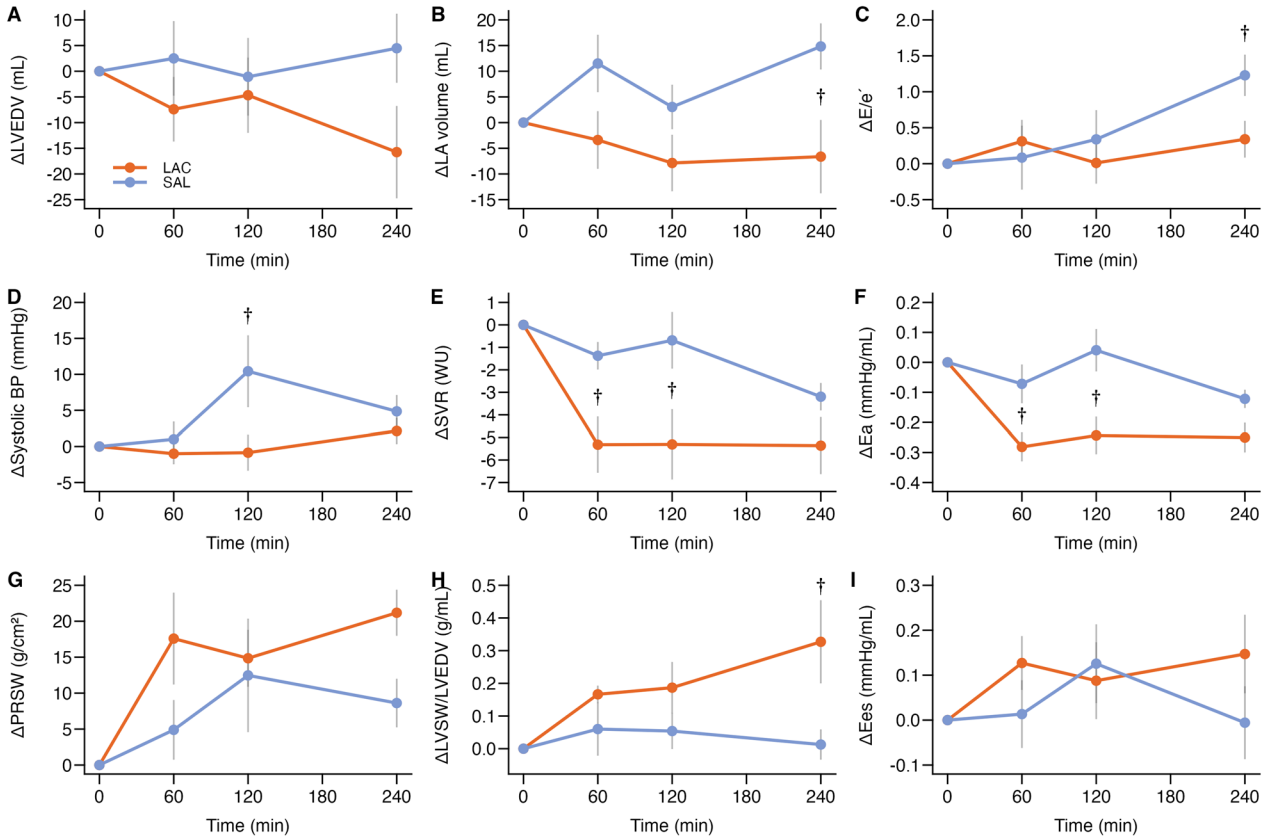

Fig. 3 Effect of each treatment on cardiac parameters. Measurements during infusion with half-molar sodium lactate (LAC) infusion and hypertonic sodium chloride (SAL). Time = 0 indicates baseline before infusion. **A–C** Preload parameters left ventricular end-diastolic volume (LVEDV), left atrial (LA) volume, and ratio of early (E) diastolic mitral inflow velocity and early diastolic mitral plane tissue velocity (e') remained lower during LAC compared with SAL infusion. **D–F** Systolic blood pressure (sBP) remained lower during LAC compared with SAL infusion and systemic vascular resistance (SVR) and arterial elastance (Ea) were significantly reduced during LAC infusion. **G–I** Contractility measures preload recruitable stroke work (PRSW) and left ventricular stroke work normalized to end-diastolic volume (LVSW/EDV) were increased during LAC infusion, while end-systolic elastance (Ees) did not differ significantly. Data are shown as mean, with bars indicating SEM. † indicates $P < 0.05$ between treatments at a given time point

Table 3 Fluid intake and output

	LAC	SAL	Difference (95% CI)	*P* value
Intravenous fluid intake, mL	1379 ± 178	1379 ± 171	0 (− 12, 12)	1.000
20% glucose intake during HEC*, mL	209 ± 53	207 ± 76	2 (− 36, 41)	0.89
Oral fluid intake, mL	1210 ± 293	1283 ± 165	− 73 (− 273, 126)	0.40
Urine output, mL	1315 ± 343	1429 ± 175	− 114 (− 436, 208)	0.43

Values are mean ± SD for each treatment and between-treatment pairwise comparison (95% CI) and associated *P* values from a mixed model, which incorporated repeated measurements.*From 180 to 240 min during the hyperinsulinemic-euglycemic clamp. LAC = half-molar sodium lactate; SAL = hypertonic sodium chloride

volume, and E/e´ remained unchanged, and both treatments involved similar volumes of intravenous fluid. During SAL infusion a rise in preload parameters was recorded, particularly at the 240-min mark (during HEC) when additional intravenous fluid was given, though in similar amounts to the LAC infusion. This likely explains the modest SAL-induced increase in CO through Frank-Starling mechanisms, along with Bainbridge reflex activation during hypertonic fluid administration, as evidenced by a similar increase in HR between LAC and SAL. Additionally, the 60-min HEC clamp could influence cardiovascular function under fasting conditions, particularly during SAL infusion, by providing additional myocardial substrate via insulin-driven glycolysis [33].

Table 4 Biomarkers

	LAC		SAL		Difference (95% CI)	*P* value
	Baseline	After treatment	Baseline	After treatment		
pH	7.35 ± 0.01	7.43 ± 0.06	7.38 ± 0.02	7.35 ± 0.02	0.12 (0.09, 0.14)	**< 0.001**
HCO_3 mmol/L	25.0 ± 1.1	29.6 ± 7.0	25.2 ± 1.3	23.5 ± 1.1	6.7 (3.7, 9.7)	**< 0.001**
pCO_2, kPa	6.8 ± 0.5	6.5 ± 0.4	6.2 ± 0.4	6.1 ± 0.4	− 0.2 (− 0.4, 0.1)	0.190
Hematcrite	44.0 ± 3.2	40.3 ± 2.2	43.7 ± 2.4	39.9 ± 2.1	0.7 (0.0, 1.3)	0.053
Sodium, mmol/L	142 ± 1	146 ± 1	141 ± 2	146 ± 1	− 1 (− 2, − 1)	**< 0.001**
Chloride, mmol/L	108 ± 2	107 ± 4	108 ± 1	117 ± 3	− 10 (− 11, − 9)	**< 0.001**
Calcium, mmol/L	1.21 ± 0.02	1.15 ± 0.03	1.22 ± 0.03	1.18 ± 0.02	− 0.03 (− 0.04, − 0.02)	**< 0.001**
Potassium, mmol/L	4.0 ± 0.1	3.6 ± 0.3	4.2 ± 0.5	4.1 ± 0.2	− 0.2 (− 0.4, − 0.1)	**0.011**

Values are mean ± SD at baseline and 4-h average for each treatment and between-treatment pairwise comparison (95% CI) and associated *P*-values from a mixed model, which incorporated repeated measurements. LAC = half-molar sodium lactate; SAL = hypertonic sodium chloride. Bold text highlights *P* values < 0.05

This enhanced glycolysis may increase pyruvate availability in the SAL group, although in the LAC group, pyruvate production was already elevated due to lactate metabolism, potentially explaining the more pronounced cardiovascular response to the HEC observed with SAL. Interestingly, while lactate may cause arterial vasorelaxation and venoconstriction in isolated vessels [34–36], it may also enhance contractility [9, 31]. This aligns with the physiological role of lactate in promoting forward flow to support organ perfusion during distress. The combination of stable preload, decreased afterload, and indices of increased contractility suggests an efficient cardiovascular adaptation with a resultant improvement in CO. These findings all highlight the potential therapeutic value of LAC in optimizing cardiac performance.

Hypertonic solutions can raise systolic blood pressure by increasing intravascular volume through osmotic shifts [4–6], enhancing preload and stroke volume. The Bainbridge effect further elevates HR in response to increased venous return. While these effects may improve perfusion pressure, they also raise the cardiac rate-pressure product, thereby increasing energy demands, which could impair cardiac function during periods of distress. Indeed, SAL infusion raised systolic blood pressure and estimated sPAP, increasing biventricular afterload. In contrast, LAC infusion maintained stable systolic pressure while lowering sPAP. Additionally, SVR and Ea were significantly reduced during LAC treatment, reflecting a beneficial decrease in afterload despite equivalent fluid administration in both groups. This fits with unaltered measures of myocardial work despite an increase in CO, indicating no adverse increase in myocardial energy metabolism [18]. These findings support previous data demonstrating a vasodilatory effect of lactate [36]. Finally, treatment with LAC may exert direct cardiac effects to improve contractile function, as evident by improvement in the less load-independent measures of contractility. As such, the underlying mechanisms driving CO enhancement are multifaceted and intricately interconnected within the complex constraints of the cardiovascular system.

Safety issues

LAC infusion caused no adverse events in the present study. Previous studies have investigated lactate administration above 10 mmol/L without causing adverse effects [37, 38]. Others have demonstrated safety of 24 h of administration in patients with decompensated heart failure [5]. Future studies with prolonged treatment are required to further investigate the safety profile of LAC treatment.

Limitations

This study included only healthy, lean men, which limits its generalizability of our findings to women and populations with altered substrate metabolism. The crossover design minimized interindividual variation but posed a potential for carryover effects, which we addressed by implementing a significant washout period between visits. Moreover, the linear mixed model adjusted for treatment order and period effects and revealed no significant interactions. We used sodium-matched saline as a control to avoid confounding due to osmolality. Although hypertonic sodium chloride and sodium-lactate solutions have similar osmolarity, their effect on tonicity may differ due to lactate metabolism. This difference in tonicity can influence physiological responses beyond lactate oxidation through chloride-related mechanisms. SAL may increase extracellular tonicity and volume, potentially mitigating the relative LAC-induced cardiovascular effects in our study [39, 40]. Furthermore, SAL infusion may cause hyperchloremic acidosis, which we, however, did not observe, whereas LAC infusion induces mild metabolic alkalosis [5, 32, 36], similar to the effects

of other monocarboxylates [41–43]. Nonetheless, studies comparing LAC to bicarbonate have shown superior improvements in CO during LAC infusion [27], and the vasodilatory effect of LAC seems to be independent of intracellular pH [44]. Thus, pH alterations are unlikely to account for the prominent cardiovascular effects observed in our study. While we did not measure levels of circulating catecholamines, previous studies did not demonstrate any effect of lactate on metanephrine levels [45, 46]. Also, we did not measure cardiac biomarkers, although these markers are expected to be normal in this cohort.

Conclusion

LAC infusion demonstrated significant cardiovascular benefits, enhancing CO and SV, improving systolic function, and reducing afterload, while maintaining stable preload parameters. These findings suggest that LAC may be a superior resuscitation fluid, particularly in patients with impaired cardiac function.

Abbreviations

BP	Blood pressure
CO	Cardiac output
E/A	Ratio of early (E) and late (A) diastolic mitral in-flow velocity
Ea	Arterial elastance
Ees	End-systolic elastance
e'	Early diastolic mitral plane tissue velocity
GLS	Global longitudinal strain
LAC	Half-molar sodium lactate
LA	Left atrial
LV	Left ventricle
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVOT	Left ventricular outflow tract
LVSW	Left ventricular stroke work
PRSW	Preload recruitable stroke work
SAL	Hypertonic sodium chloride
S'max	Peak systolic velocity
sPAP	Systolic pulmonary artery pressure
SV	Stroke volume
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05259-0.

Additional file 1 (DOCX 15 KB)

Author contribution

KBH, NG, MGBP, NR, ES, NM drafted the protocol. KBH, NG, and RN drafted the manuscript. MGBP recruited patients and MGBP, KBH, and NG performed the investigations. JTN, KBH, and NG analyzed the data. KBH, NG, MGBP, NR, JTN, ES, NM, HW, RN contributed to designing the study, interpreting the data, and writing the manuscript. All authors contributed considerable in revising the manuscript and approved the final version.

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Data availability

Data supporting this work will be shared upon reasonable request to the corresponding author.

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.

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