# The comparative effects of 3% saline and 0.5M sodium lactate on cardiac function: a randomised, crossover study in volunteers

Marek Nalos, Euguenia Kholodniak, Louise Smith, Sam Orde, Iris Ting, Michel Slama, Ian Seppelt, Anthony S McLean and Stephen Huang


## ABSTRACT

**Objective:** To investigate the metabolic and cardiac effects of intravenous administration of two hypertonic solutions — 3% saline (SAL) and 0.5M sodium lactate (LAC).

**Design, setting and participants:** A randomised, double-blind, crossover study in ten human volunteers. Intravenous bolus of either SAL or LAC at 3 mL/kg over 20 min followed by a 2 mL/kg infusion over 60 min.

**Main outcome measures:** Acid base parameters and echocardiographic indices of cardiac function, cardiac output (CO), left ventricular ejection fraction (LVEF) and mitral annular peak systolic velocity (Sm) before and after infusion of SAL or LAC.

**Results:** Despite haemodilution, we observed an increase in sodium (139 ± 2 mmol/L to 142 ± 2 mmol/L in both groups) and respective anions, chloride (106 ± 2 mmol/L to 112 ± 3 mmol/L) and lactate (1.01 ± 0.28 mmol/L to 2.38 ± 0.38 mmol/L) with SAL and LAC, respectively. The pH (7.37 ± 0.03 to 7.45 ± 0.03; $P < 0.01$) and simplified strong ion difference (SID) (36.3 ± 4.6 mmol/L to 39.2 ± 3.6 mmol/L; $P < 0.01$) increased during the LAC infusion. The pH was unchanged, but SID decreased during SAL infusion (36.3 ± 2.5 mmol/L to 33.9 ± 3.1 mmol/L; $P = 0.01$). Both solutions led to an increase in preload and cardiac function, CO (4.36 ± 0.79 L/min to 4.98 ± 1.37 L/min *v* 4.62 ± 1.30 L/min to 5.13 ± 1.44 L/min), LVEF (61 ± 6% to 63 ± 8% *v* 64 ± 6% to 68 ± 7%). The averaged Sm improved in the LAC group as compared with the SAL group (0.088 ± 0.008 to 0.096 ± 0.016 *v* 0.086 ± 0.012 to 0.082 ± 0.012; $P = 0.032$).

**Conclusions:** The administration of SAL or LAC has opposing effects on acid base variables such as SID. Hypertonic fluid infusion lead to increased cardiac preload and performance with Sm, suggesting better left ventricular systolic function during LAC as compared with SAL. Lactated hypertonic solutions should be evaluated as resuscitation fluids.


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Fluid resuscitation is common in critical care, but the liberal use of fluid boluses has come under scrutiny given the association between positive fluid balance and worse outcomes.[1] The use of hypertonic crystalloid solutions for fluid resuscitation may be advantageous, as lower volumes are required to achieve similar haemodynamic effects while avoiding the concerning side effects of colloid solutions.[2,3] In this study we evaluate the effects of two hypertonic solutions on cardiac function and acid base variables in human volunteers. Both 0.5M sodium lactate (LAC) (Totilac, Innogene Kalbiotech, Singapore) and 3% saline (SAL) (AHB1354, Baxter, Old Toongabbie, NSW, Australia) solutions are used in neurocritical care for the management of raised intracranial pressure, but they may also be used as resuscitation fluids peri-operatively and in sepsis.[2,4-7] The two solutions contain a similar amount of sodium (504 mmol/L *v* 513 mmol/L, LAC *v* SAL, respectively) but differ in the accompanying anion, lactate in LAC (504 mmol/L) and chloride (513 mmol/L) in SAL. We speculated that there may be differential effects on cardiac function between the two solutions. Lactate has traditionally been considered to have a depressant effect on myocardial contractility,[8] but infusion of LAC was associated with improved cardiac function after cardiac surgery and in acute decompensated heart failure.[6,9] The relative hyperchloraemia during SAL infusion is associated with metabolic acidosis and may itself have a cardio-depressant effect;[8,10] however, infusion of hypertonic saline increases preload and endogenous catecholamines in healthy patients and may thus indirectly enhance inotropy.[11,12]

We used a comprehensive echocardiographic examination and sequential venous blood gas analysis to investigate the metabolic and cardiac effects of a bolus followed by 60 minutes of maintenance infusion of LAC and SAL in healthy volunteers.

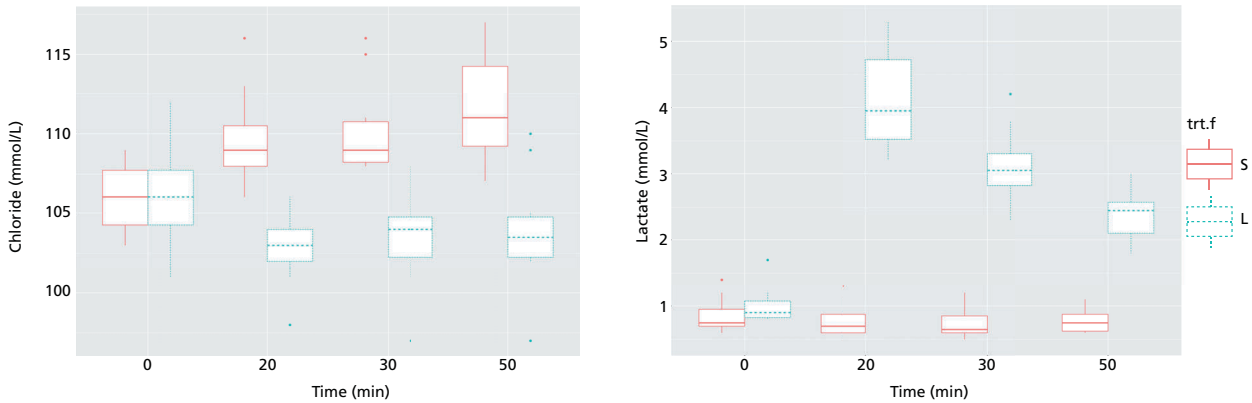
## Methods

Ten healthy volunteers (four women, six men; age, 29–64 years; weight, 64–100 kg) were recruited from intensive

care unit colleagues for the study after informed consent. Formal ethics approval was not sought. Each volunteer fasted for at least 6 hours before the study procedure. On the study day, each volunteer was randomly assigned to receive either SAL or LAC solution. Both left and right cubital veins were cannulated while the patient was resting supine in a quiet room. Baseline venous blood gas was obtained. A pulse oximeter device was applied to a finger of the subject's right hand while a blood pressure cuff was applied to the left arm. Both electrocardiogram and plethysmography signals were used to measure heart rate. All devices were connected to a bedside monitor (Spacelabs Medical 90309, Snoqualmie, WA, USA). A comprehensive transthoracic echocardiogram (TTE) (Acuson S3000, Siemens, Erlangen, Germany) using a pre-specified standard protocol was performed by a sonographer before the infusion. An intravenous infusion of either SAL or LAC was then commenced with a bolus of 3 mL/kg over 20 minutes and continued for another 60 minutes at an infusion rate of 2 mL/kg/hour to maintain steady state. Ten minutes into the continuous infusion a second comprehensive TTE was performed to evaluate the effects of the respective solutions on cardiac function while the maintenance infusion was ongoing. Further measurements of blood pressure, heart rate, oxygen saturation ($Spo_2$) and venous blood gas were taken at the end of fluid bolus, before and at the end of the second TTE. Venous blood gas samples were placed on ice and promptly analysed on a blood gas analyser (ABL800 FLEX, Radiometer, Copenhagen, Denmark).

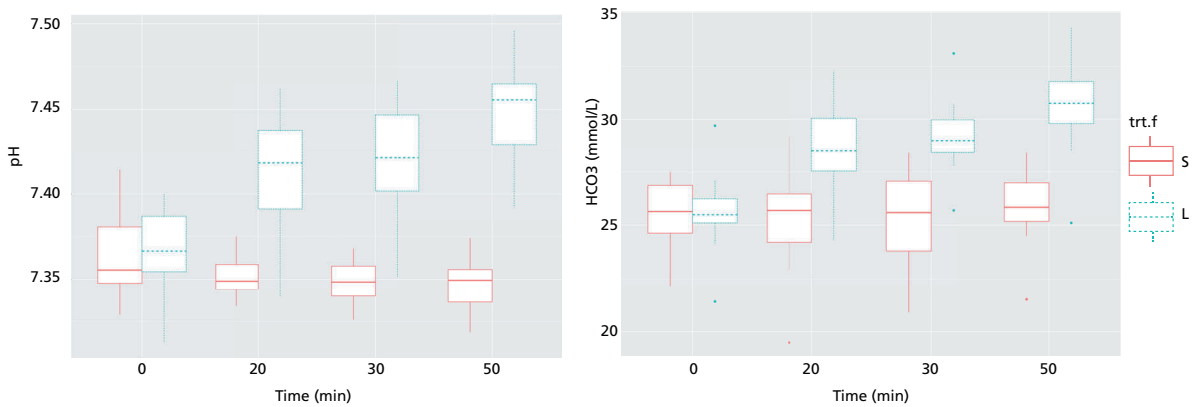
Each participant was crossed over to the other solution

**Figure1. Effects of hypercapnic acidosis on immune function**




L = LAC. S = SAL. trt.f = (treatment factor). * Median, interquartile range, and minimum–maximum range.

**Figure 2. Effect of 3% sodium chloride (SAL) or 0.5M sodium lactate (LAC) on venous blood pH and calculated $HCO_3^-$***




$HCO_3^-$ = bicarbonate. L = LAC. S = SAL. trt.f = (treatment factor). * Median, interquartile range, and minimum–maximum range

**Table 1. Acid base variables in peripheral venous blood**

| | | pH | $Pvco_2$ (mmHg) | $HCO_3^-$ (mmol/L) | Hb (g/L) | Hct (%) | $Na^+$ (mmol/L) | $Chloride^-$ (mmol/L) | $K^+$ (mmol/L) | Lactate (mmol/L) | SID (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LAC | Baseline | 7.37 ± 0.03 | 46.1 ± 6.5 | 25.6 ± 2.1 | 138 ± 11 | 42.6% ± 3.3% | 139 ± 2 | 106 ± 3 | 4.0 ± 0.2 | 1.01 ± 0.28 | 36.3 ± 4.6 |
| | Bolus | 7.41 ± 0.04 | 45.5 ± 6.1 | 28.5 ± 2.3 | 131 ± 9 | 40.5% ± 2.7% | 142 ± 2 | 103 ± 2 | 3.9 ± 0.2 | 4.09 ± 0.72 | 38.6 ± 3.2 |
| | 10 min after bolus | 7.42 ± 0.04 | 45.8 ± 5.7 | 29.2 ± 1.9 | 132 ± 10 | 40.7% ± 2.9% | 142 ± 2 | 103 ± 3 | 3.8 ± 0.2 | 3.14 ± 0.55 | 39.0 ± 3.8 |
| | End of infusion | 7.45 ± 0.03 | 45.5 ± 6.8 | 30.7 ± 2.7 | 134 ± 12 | 41.0% ± 2.9% | 142 ± 2 | 104 ± 4 | 3.8 ± 0.4 | 2.38 ± 0.38 | 39.2 ± 3.6 |
| SAL | Baseline | 7.36 ± 0.03 | 47.1 ± 6.9 | 25.5 ± 1.6 | 137 ± 9 | 42.0% ± 2.5% | 139 ± 2 | 106 ± 2 | 4.0 ± 0.1 | 0.85 ± 0.27 | 36.3 ± 2.5 |
| | Bolus | 7.35 ± 0.01 | 47.4 ± 5.0 | 25.2 ± 2.6 | 129 ± 8 | 39.8% ± 2.2% | 142 ± 1 | 110 ± 3 | 3.9 ± 0.2 | 0.78 ± 0.25 | 35.1 ± 2.2 |
| | 10 min after bolus | 7.35 ± 0.01 | 48.2 ± 5.1 | 25.4 ± 2.4 | 129 ± 9 | 39.7% ± 2.0% | 142 ± 2 | 110 ± 3 | 4.0 ± 0.2 | 0.72 ± 0.22 | 34.6 ± 1.7 |
| | End of infusion | 7.35 ± 0.02 | 48.2 ± 5.0 | 25.7 ± 1.8 | 131 ± 10 | 40.3% ± 3.1% | 142 ± 2 | 112 ± 3 | 4.1 ± 0.3 | 0.77 ± 0.16 | 33.9 ± 3.1 |

Hb = haemoglobin. $HCO_3^-$ = bicarbonate. Hct = haematocrit. $K^+$ = potassium ion. LAC = 0.5M sodium lactate. $Na^+$ = sodium ion. $Pvco_2$ = venous partial pressure of carbon dioxide. SAL = 3% sodium chloride. SID = simplified strong ion difference.

one week later at the earliest. The order of the solutions was determined randomly by a dedicated researcher not involved in the study procedures. The participants, sonographers, fluid administering, and echocardiogram evaluating researchers were blinded to the randomisation order.

A linear mixed effects model was used for analysis of a two-treatment and two-period crossover study design.[13] Treatment (SAL *v* LAC), time and an interaction terms (treatment against time) were incorporated as fixed effect variables, whereas subjects and the treatment sequence were included as random effects. In case of longitudinal data with more than two time points, a second order polynomial term was also included in the model to account for any transient (non-linear) temporal changes where appropriate. Model parameters were estimated using maximal likelihood estimation. Kenward–Roger approximations were used in overall significance test of the model (*F* test) and in testing for parameters significance (*t* test) after refitting the model with restricted maximum likelihood.[14] Exact restricted likelihood ratio test was used for testing significance of individual and sequence (crossover) effects.

Data are presented as mean ± standard deviation (SD). Model parameters and test statistics are presented as mean ± standard error (SE) or mean (upper, lower, 95% confidence interval [CI]).[15] All analyses were carried out using the open source software R (version 3.3.1) (The R Foundation for Statistical Computing, Austria). We considered a change in cardiac output of 0.3 L/min as clinically significant. Assuming between-treatment and within-treatment change score standard deviations were 0.5 L/min, and $\alpha = 0.05$ and power of 0.8, the required sample size was ten subjects.

**Table 2. Linear mixed effects model results for acid base data**

| | Treatment effects | Time effects | Interaction effect |
|---|---|---|---|
| pH | $P = 0.181$ | $P = 0.024$ | $P < 0.001$ |
| $Pvco_2$ (mmHg) | $P = 0.002$ | $P = 0.659$ | na |
| $HCO_3^-$ (mmHg) | $P = 0.163$ | $P = 0.618$ | $P < 0.001$ |
| Hb (g/L) | $P = 0.016$ | $P < 0.001$ | na |
| $Na^+$ (mmol/L) | $P = 0.929$ | $P < 0.001$ | Na |
| $Cl^-$ (mmol/L) | $P = 0.012$ | $P < 0.001$ | $P < 0.001$ |
| $K^+$ (mmol/L) | $P = 0.026$ | $P = 0.005$ | $P < 0.001$ |
| $Lactate^-$ (mmol/L) | $P < 0.001$ | $P < 0.001$ | $P < 0.007$ |
| Hct | $P = 0.124$ | $P < 0.001$ | na |
| SID (mmol/L) | $P = 0.405$ | $P = 0.013$ | $P < 0.001$ |

Hb = haemoglobin. $HCO_3^-$ = bicarbonate. Hct = haematocrit. $K^+$ = potassium ion. $Na^+$ = sodium ion. $Pvco_2$ = venous partial pressure of carbon dioxide. SID = simplified strong ion difference.

## Results

As expected, the plasma levels of chloride and lactate increased significantly after SAL and LAC solutions infusion, respectively (Figure 1). Sodium level increased, while haemoglobin levels and haematocrit were reduced by both solutions, consistent with the haemodilution effect of hypertonic fluids, without a significant differential effect between SAL and LAC. The pH, bicarbonate and simplified strong ion difference (SID) significantly increased while potassium levels significantly decreased during LAC infusion (Figure 2). The venous partial pressure of carbon dioxide ($Pvco_2$) was slightly higher, while SID was significantly reduced during SAL infusion (Table 1 and Table 2).

**Table 3. Echocardiographic indices of left and right ventricular systolic function before and during infusion of the respective hypertonic solutions**

| | LVEDD (mm) | LVESD (mm) | LVEF (%) | CO (L/min) | LV Sm lat (m/s) | LV Sm med (m/s) | TAPSE (cm) |
|---|---|---|---|---|---|---|---|
| LAC | | | | | | | |
| Before | 46.6 ± 5.5 | 29.2 ± 10.2 | 64% ± 6% | 4.62 ± 1.30 | 0.10 ± 0.01 | 0.08 ± 0.01 | 2.41 ± 0.59 |
| After | 47.0 ± 5.3 | 28.0 ± 9.9 | 68% ± 7% | 5.13 ± 1.44 | 0.11 ± 0.02 | 0.09 ± 0.01 | 2.51 ± 0.41 |
| SAL | | | | | | | |
| Before | 47.7 ± 4.3 | 31.0 ± 4.8 | 60.8% ± 5.5% | 4.36 ± 0.79 | 0.09 ± 0.02 | 0.08 ± 0.01 | 2.36 ± 0.40 |
| After | 48.2 ± 3.4 | 28.6 ± 10.1 | 62.9% ± 7.8% | 4.98 ± 1.37 | 0.08 ± 0.01 | 0.08 ± 0.01 | 2.46 ± 0.34 |

CO = cardiac output. LAC = 0.5M sodium lactate. LVEDD = left ventricular end diastolic diameter. LVEF = left ventricular ejection fraction. LVESD = left ventricular end systolic diameter. LV Sm lat = lateral mitral annular peak systolic velocity (tissue Doppler imaging). LV Sm med = medial mitral annular peak systolic velocity (tissue Doppler imaging). m/s = meter/second. SAL = 3% sodium chloride. TAPSE = tricuspid annular plane systolic excursion.

**Table 4. Three-dimensional (3D) echocardiography parameters before and during infusion of the respective hypertonic solutions**

| | 3D LVEF | 3D RVEF | 3D LV GLS | 3D LV GCS | 3D LV twist | 3D LV torsion |
|---|---|---|---|---|---|---|
| LAC | | | | | | |
| Before | 58.1% ± 6.5% | 45.7% ± 9.0% | –18% | –23.6% | 10.7% ± 6.7% | 1.28% ± 0.83% |
| After | 61.6% ± 5.9% | 49.5% ± 7.5% | –20.1% | –25.2% | 16.1% ± 5.9% | 1.86% ± 0.76% |
| SAL | | | | | | |
| Before | 60.5% ± 4.8% | 52.6% ± 7.3% | –16.9% | –26% | 11.5% ± 6.0% | 1.33% ± 0.69% |
| After | 63.1% ± 5.1% | 50.3% ± 7.1% | –19.1% | –27.1% | 16.0% ± 5.6% | 1.93% ± 0.71% |

LAC = 0.5M sodium lactate. LV = left ventricle. LV GCS = left ventricular global circumferential strain. LV GLS = left ventricular global longitudinal strain. LVEF = left ventricular ejection fraction. RVEF = right ventricular ejection fraction. SAL = 3% sodium chloride.

There were no significant differences in any haemodynamic parameters or in the measured TTE parameters between the respective solutions, apart from averaged (septal and lateral) mitral annular peak systolic velocity on tissue Doppler imaging in the LAC group compared with the SAL group (0.088 ± 0.008 to 0.096 ± 0.016 *v* 0.086 ± 0.012 to 0.082 ± 0.012; $P = 0.032$) (Table 3 and Table 4). Both solutions led to an increase in left ventricular (LV) end diastolic diameter and volume, tricuspid annular plane systolic excursion, LV ejection fraction, LV stroke volume, and cardiac output. Stroke volume was slightly higher in most volunteers when LAC was infused, but this was not statistically significant (Table 5).

## Discussion

The main findings of our study are that a bolus infusion of sodium-containing hypertonic solutions (SAL or LAC) of 3 mL/kg followed by a maintenance infusion of 1 mL/kg for about 60 minutes lead to increased plasma sodium and haemodilution, as expected. Consequently, both solutions increased preload as judged by increased LV end diastolic diameter and volume. Infusion of both solutions was associated with an increase in cardiac performance, as tricuspid annular plane systolic excursion, LV ejection fraction, stroke volume and cardiac output increased. The only statistically significant difference between SAL and LAC infusions was the small increase in mitral annular peak systolic velocity, the clinical significance of which is unclear. While it is likely that an increase in intravascular fluid volume accounted for the cardiac effects, other endocrine and metabolic effects, such as lactate oxidation by the myocardium, may have also contributed.[16,17]

Following the bolus and maintenance infusion of SAL, chloride levels significantly increased. In contrast, during LAC infusion, chloride decreased while lactate levels,

**Table 5. Absolute changes and significance values for echocardiography data before and during infusion of the respective hypertonic solutions**

| | SAL mean (SD) | LAC mean (SD) | Difference mean (SE) | *P* |
|---|---|---|---|---|
| CO (L/min) | 0.63 (0.89) | 0.52 (0.51) | –0.11 (0.28) | 0.7180 |
| HR (per min) | 3.1 (4.1) | 0.5 (5.9) | –2.6 (2.1) | 0.2376 |
| SV (mL) | 5.2 (6.9) | 6.9 (9.5) | 1.7 (4.1) | 0.705 |
| TAPSE (cm) | 0.1 (0.3) | 0.0 (0.5) | –0.06 (0.18) | 0.758 |
| LV Sm (m/s) | –0.05 (0.11) | 0.08 (0.11) | 0.13 (0.05) | 0.032 |
| LVEF (%) | 2.1 (8.0) | 4.3 (5.6) | 2.2 (1.9) | 0.299 |
| LVEDD (mm) | 0.6 (3.3) | 0.4 (2.0) | –0.2 (1.2) | 0.882 |
| E/e' | –0.2 (1.4) | 0.0 (1.7) | 0.2 (0.6) | 0.719 |
| LV GLS | –1.78% (3.93%) | –1.88% (2.74%) | –0.10% (1.05%) | 0.930 |
| LV GCS | –2.24% (3.49%) | –1.28% (5.94%) | 0.967% (1.78%) | 0.623 |
| Twist | 3.83% (5.51%) | 5.40% (8.15%) | 1.57% (2.71%) | 0.589 |
| Torsion | 0.51% (0.65%) | 0.59% (1.01%) | 0.08% (0.337%) | 0.828 |

CO = cardiac output. E/e' = Index of diastolic function (early diastolic trans-mitral peak flow to annular tissue peak velocity. HR = heart rate. LAC = 0.5M sodium lactate. LVEDD = left ventricular end diastolic diameter. LVEF = left ventricular ejection fraction. LV GCS = left ventricular global circumferential strain. LV GLC = left ventricular global longitudinal strain. LV Sm = averaged mitral annular peak systolic velocity (tissue Doppler imaging). SAL = 3% sodium chloride. SD = standard deviation. SE = standard error. SV = stroke volume. TAPSE = tricuspid annular plane systolic excursion.

bicarbonate, pH and SID increased. While we showed that in comparison to SAL, LAC had only a limited additional positive effect on cardiac function in healthy resting patients, we can safely postulate that elevated lactate levels per se have no detrimental effect on cardiac function, as assessed by comprehensive TTE. The effects on cardiac function, however, might be different in patients subjected to the stress of critical illness, as the proportion of ATP production from lactate may potentially increase in such situations.[18,19] This assertion is supported by studies documenting improved cardiac performance in patients with acute decompensated heart failure and after cardiac surgery.[6,9] However, the results of two animal studies using hypertonic lactate for resuscitation of septic shock are disparate.[20,21] Using a non-lethal model of porcine septic shock, Duburcq and colleagues[20] were able to show improved haemodynamics, while in a lethal model of porcine septic shock, Su and colleagues[21] concluded that lactate hastens the demise of shocked animals. While this may seem contradictory at first glance, both studies illustrate the concept of lactate shuttle.[22] When shock is severe enough to disrupt the ability of mitochondria to metabolise lactate in the majority of tissues, raising extracellular lactate level will undoubtedly impair cellular lactate export, thereby impairing intracellular acidosis and cellular function. But when the majority of mitochondria are able to metabolise lactate, the provision of the essential substrate becomes beneficial. The only study in human septic shock by Somasetia and colleagues[23] suggests that hypertonic lactate infusion may indeed be beneficial.

The metabolic alkalosis and hypokalaemia were expected after LAC infusion. The infused lactate becomes a quantitatively relevant substrate for mitochondrial oxidation in the myocardium and brain, in addition to the usual gluconeogenic metabolism by the liver and kidney.[24] Once the lactate contained in LAC is metabolised, the strong ion sodium increases the plasma SID leading to rise in plasma bicarbonate. One would expect the $Pco_2$ to rise in proportion with bicarbonate; however, interestingly, the venous $Pco_2$ tended to be higher during SAL infusion. This may have implications for the treatment of intracranial hypertension, as hypercarbia and acidosis increase cerebral blood flow and intracranial pressure. Both SAL and LAC were evaluated in patients with traumatic brain injury and were found superior to 20% mannitol.[4,25-27] Our results suggest that LAC may be favoured over SAL for the treatment of raised intracranial pressure because it is not associated with a rise in $Pvco_2$ and has an alkalinising effect. Therefore, LAC infusion may be the preferred treatment for intracranial hypertension as has been shown.[28]

Fluid resuscitation with hypertonic solutions has been investigated in animals, healthy humans and various patient populations.[2,7,11,29,30] Our results for both SAL and LAC are in agreement with other studies, showing an expansion of intravascular volume, increased preload, stroke volume and cardiac output by hypertonic solutions.[2,11,12,30-32] We were also able to demonstrate that, in healthy humans, the effect is similar when lactate instead of chloride is used to accompany the sodium ion. Compared with conventional "plasma expanders", both hypertonic solutions are inexpensive and without risk of kidney injury, coagulopathy, anaphylaxis or transmission of infectious diseases.[2,3] Ongoing research into their efficacy in various critical ill patients is warranted.

Our study has several limitations. First, the volunteers comprised a small, heterogeneous group of health care professionals with a relatively wide range of age, weight and fitness. The effects of both solutions may have been influenced by their baseline characteristics, in particular the level of fitness.[33] Second, as the participants were all healthy in this study, the applicability of our results to critically ill patients with deranged physiology is unclear. Third, we used a blood gas analyser rather than a dedicated blood cell counter and electrolyte measuring device to measure electrolytes, haemoglobin and haematocrit levels, which may have influenced absolute values.

## Conclusions

In summary, the bolus infusion of SAL or LAC in resting healthy humans led to haemodilution, an increase in intravascular blood volume and cardiac preload, and improved cardiac performance, with no detrimental effect on LV systolic function during LAC infusion. The increase in blood sodium was similar in both groups but limited by the expected fluid shifts due to increased plasma tonicity. Mild metabolic alkalosis and hypokalaemia was associated with LAC infusion, while mild hyperchloraemia and hypercarbia were associated with the infusion of SAL. Further investigations of hypertonic sodium-containing solutions in the critically ill may lead to designing safe and effective resuscitation fluids.

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## Competing interests

None declared.

## Author details

Marek Nalos[1,3]
Euguenia Kholodniak[2]
Louise Smith[2]
Sam Orde[1,2]
Iris Ting[2]
Michel Slama[5,6]
Ian Seppelt[1,3,4]
Anthony S McLean[1,2,3]
Stephen Huang[1,2,3]

1 Department of Intensive Care Medicine, Nepean Hospital, Sydney, NSW, Australia.
2 The Cardiovascular Ultrasound Laboratory, Nepean Hospital, Sydney, NSW, Australia.
3 Nepean Clinical School, University of Sydney, Sydney, NSW, Australia.
4 Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia.
5 Réanimation Médicale, CHU Amiens-Picardie, Amiens, France.
6 INSERM 1088, Université de Picardie Jules Verne, Amiens, France.

***Correspondence:*** mareknalos@gmail.com

## References

1 Mitchell KH, Carlbom D, Caldwell E, et al. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. *Ann Am Thorac Soc* 2015; 12: 1837-44.
2 Pfortmueller CA, Schefold JC. Hypertonic saline in critical illness — a systematic review. *J Crit Care* 2017; 42: 168-77.
3 Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38–0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ* 2013; 346: f839.
4 Ichai C, Armando G, Orban JC, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med* 2009; 35: 471-9.
5 Burgess S, Abu-Laban RB, Slavik RS, et al. A systematic review of randomized controlled trials comparing hypertonic sodium solutions and mannitol for traumatic brain injury: implications for emergency department management. *Ann Pharmacother* 2016; 50: 291-300.
6 Leverve XM, Boon C, Hakim T, et al. Half-molar sodium-lactate solution has a beneficial effect in patients after coronary artery bypass grafting. *Intensive Care Med* 2008; 34: 1796-803.
7 Fang ZX, Li YF, Zhou XQ, et al. Effects of resuscitation with crystalloid fluids on cardiac function in patients with severe sepsis. *BMC Infect Dis* 2008; 8: 50.
8 Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med* 2014; 371: 2309-19.
9 Nalos M, Leverve X, Huang SJ, et al. Half-molar sodium lactate infusion improves cardiac performance in acute heart failure: a pilot randomised controlled clinical trial. *Crit Care* 2014; 18: R48.
10 Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; 308: 1566-72.
11 Farquhar WB, Paul EE, Prettyman AV, Stillabower ME. Blood pressure and hemodynamic responses to an acute sodium load in humans. *J Appl Physiol (1985)* 2005; 99: 1545-51.

12 Svensén C, Hahn RG. Volume kinetics of Ringer solution, dextran 70, and hypertonic saline in male volunteers. *Anesthesiology* 1997; 87: 204-12.

13 Putt M, Chinchilli VM. A mixed effects model for the analysis of repeated measures cross-over studies. *Stat Med* 1999; 18: 3037-58.

14 Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997; 53: 983-97.

15 Wasserstein RL, Lazar NA. The ASA's statement on *P*-values: context, process, and purpose. *Am Stat* 2016; 70: 129-33.

16 Jensen JM, Mose FH, Bech JN, et al. Effect of volume expansion with hypertonic- and isotonic saline and isotonic glucose on sodium and water transport in the principal cells in the kidney. *BMC Nephrol* 2013; 14: 202.

17 Lloyd S, Brocks C, Chatham JC. Differential modulation of glucose, lactate, and pyruvate oxidation by insulin and dichloroacetate in the rat heart. *Am J Physiol Heart Circ Physiol* 2003; 285: H163-72.

18 Gertz EW, Wisneski JA, Stanley WC, Neese RA. Myocardial substrate utilization during exercise in humans: dual carbon-labeled carbohydrate isotope experiments. *J Clin Invest* 1988; 82: 2017-25.

19 Kline JA, Thornton LR, Lopaschuk GD, et al. Lactate improves cardiac efficiency after hemorrhagic shock. *Shock* 2000; 14: 215-21.

20 Duburcq T, Favory R, Mathieu D, et al. Hypertonic sodium lactate improves fluid balance and hemodynamics in porcine endotoxic shock. *Crit Care* 2014; 18: 467.

21 Su F, Xie K, He X, et al. The harmful effects of hypertonic sodium lactate administration in hyperdynamic septic shock. *Shock* 2016; 46: 663-71.

22 Brooks GA. Cell-cell and intracellular lactate shuttles. *J Physiol* 2009; 587: 5591-600.

23 Somasetia DH, Setiati TE, Sjahrodji AM, et al. Early resuscitation of dengue shock syndrome in children with hyperosmolar sodium-lactate: a randomized single-blind clinical trial of efficacy and safety. *Crit Care* 2014; 18: 466.

24 van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf)* 2010; 199: 499-508.

25 Alnemari AM, Krafcik BM, Mansour TR, Gaudin D. A comparison of pharmacologic therapeutic agents used for the reduction of intracranial pressure following traumatic brain injury. *World Neurosurg* 2017; 106: 509-28.

26 Mangat HS, Chiu YL, Gerber LM, et al. Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. *J Neurosurg* 2015; 122: 202-10.

27 Mangat HS, Chiu YL, Gerber LM, et al. Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. *J Neurosurg* 2015; 122: 202-10.

28 Ichai C, Payen JF, Orban JC, et al. Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. *Intensive Care Med* 2013; 39: 1413-22.

29 Shrum B, Church B, McArthur E, et al. Hypertonic salt solution for peri operative fluid management. *Cochrane Database Syst Rev* 2016; (6): CD005576.

30 Wan L, Bellomo R, May CN. The effects of normal and hypertonic saline on regional blood flow and oxygen delivery. *Anesth Analg* 2007; 105: 141-7.

31 Baraka A, Taha S, Ghabach M, et al. Hypertonic saline prehydration in patients undergoing transurethral resection of the prostate under spinal anaesthesia. *Br J Anaesth* 1994; 72: 227-8.

32 Muller L, Lefrant JY, Jaber S, et al. Short term effects of hypertonic saline during severe sepsis and septic shock. *Ann Fr Anesth Reanim* 2004; 23: 575-80.

33 San-Millán I, Brooks GA. Assessment of metabolic flexibility by means of measuring blood lactate, fat, and carbohydrate oxidation responses to exercise in professional endurance athletes and less-fit individuals. *Sports Med* 2018; 48: 467-79. ❑