Molar Sodium Lactate Attenuates the Severity of Postcardiac Arrest Syndrome: A Preclinical Study

Neven Stevic, MD, MSc[1,2]
Laurent Argaud, MD, PhD[1,2]
Joseph Loufouat, PhD[1]
Louis Kreitmann, MD, MSc[1,2]
Laurent Desmurs, MD[3]
Michel Ovize, MD, PhD[1,2]
Gabriel Bidaux, PhD[1]
Martin Cour, MD, PhD[1,2]

OBJECTIVES: To determine whether continuous IV infusion of molar sodium lactate would limit cardiac arrest–induced neurologic injury and cardiovascular failure.

DESIGN: Randomized blinded study (animal model).

SETTING: University animal research facility.

SUBJECTS: Twenty-four adult male "New Zealand White" rabbits.

INTERVENTIONS: Anesthetized rabbits underwent 12.5 minutes of asphyxial cardiac arrest and were randomized to receive either normal saline (control group, $n = 12$) or molar sodium lactate (molar sodium lactate group, $n = 12$) at a rate of 5 mL/kg/hr during the whole 120-minute reperfusion period.

MEASUREMENTS AND MAIN RESULTS: Pupillary reactivity (primary outcome), levels of S100β protein, in vitro brain mitochondria functions, cardiovascular function, and fluid balance were assessed. Molar sodium lactate reduced brain injury, with a higher proportion of animals exhibiting pupillary reactivity to light (83% vs 25% in the CTRL group, $p = 0.01$) and lower S100β protein levels (189 ± 42 vs 412 ± 63 pg/mL, $p < 0.01$) at the end of the protocol. Molar sodium lactate significantly prevented cardiac arrest–induced decrease in oxidative phosphorylation and mitochondrial calcium–retention capacity compared with controls. At 120 minutes of reperfusion, survival did not significantly differ between the groups (10/12, 83% in the molar sodium lactate group vs nine of 12, 75% in the control group; $p > 0.99$), but hemodynamics were significantly improved in the molar sodium lactate group compared with the control group (higher mean arterial pressure [49 ± 2 vs 29 ± 3 mm Hg; $p < 0.05$], higher cardiac output [108 ± 4 vs 58 ± 9 mL/min; $p < 0.05$], higher left ventricle surface shortening fraction [38% ± 3% vs 19% ± 3%; $p < 0.05$], and lower left ventricular end-diastolic pressure [3 ± 1 vs 8 ± 2 mm Hg; $p < 0.01$]). While fluid intake was similar in both groups, fluid balance was higher in control animals (11 ± 1 mL/kg) than that in molar sodium lactate-treated rabbits (1 ± 3 mL/kg; $p < 0.01$) due to lower diuresis.

CONCLUSIONS: Molar sodium lactate was effective in limiting the severity of the postcardiac arrest syndrome. This preclinical study opens up new perspectives for the treatment of cardiac arrest.

KEY WORDS: brain mitochondria; cardiac arrest; postcardiac arrest syndrome; sodium lactate

Cardiac arrests (CAs) are responsible for more than 300,000 potentially avoidable deaths annually in both the United States and Europe, and remain a major public health issue in industrialized countries (1, 2). Mortality following resuscitated CA is due to the post-CA syndrome (3), defined as multiple organ failure including cardiovascular dysfunction and neurologic injury occurring after restoration of spontaneous circulation (ROSC)

DOI: 10.1097/CCM.0000000000005233

(4). Apart from therapeutic hypothermia, there is no intervention available to attenuate the severity of the post-CA syndrome and improve organ function (5). Therefore, there is an urgent need to investigate new therapeutic approaches to improve outcomes after CA.

For decades, hypertonic sodium lactate has been used in routine to reverse the arrhythmogenic effects of drug overdose with membrane stabilizing effects (e.g., tricyclic antidepressant) (6). Interestingly, in the 1950s, several case reports described that hypertonic sodium lactate might help restore organized cardiac rhythm after inhospital CA of various etiologies (7–9). More recently, accumulating preclinical and clinical evidences showed that exogenous hypertonic sodium lactate had beneficial effects in shock states, cardiac surgery, acute heart failure, or even after traumatic brain injury, independently of both osmotic and alkalinizing properties (10–16). As lactate is readily oxidizable (unlike glucose), in situations of energy crisis, high dose of this energetic substrate may indeed improve both cardiac performance and brain function (16–18).

Despite strong rational, the beneficial effects of sodium lactate as an adjunctive therapy after resuscitated CA have not been investigated. In the present preclinical study, we hypothesized that molar sodium lactate (MSL) would reduce the severity of the post-CA syndrome compared with the usual postresuscitation care.

MATERIALS AND METHODS

All experiments were approved by the "Comité en experimentation animale de l'université" Claude Bernard Lyon I (committee for animal research, N°055) and the French "Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation."

Surgical Preparation

As previously described, adult male "New Zealand White" rabbits were anesthetized with 5-mg/kg xylazine and 50-mg/kg ketamine (19–22). Before surgery, an IV bolus of 10-µg/kg fentanyl was administered. A tracheotomy was performed, and animals underwent mechanical ventilation with 30% FIO_2, 10-mL/kg tidal volume, and a respiratory rate of 35 breaths/min. End-tidal carbon dioxide ($ETCO_2$) concentration was measured continuously. Esophageal temperature was monitored and kept within physiologic range using a heating pad. Sixteen-gauge catheters were inserted in the right internal jugular vein and carotid. A thoracotomy was performed to expose the heart. A catheter was placed into the bladder to record urinary output (23).

Cardiac Arrest Model

A well-validated CA model was used (19–22). Briefly, primary asphyxial CA was induced by the withdrawal of mechanical ventilation in paralyzed animals with 0.3-mg/kg IV cisatracurium. After 12.5 minutes of untreated CA, cardiopulmonary resuscitation (CPR), performed by an investigator blinded to the intervention, was started with the resumption of mechanical ventilation with 100% FIO_2, cardiac massage at a rate of 150–200/min, and an IV bolus of 10-µg/kg epinephrine every 3–5 minutes until ROSC (defined as the restoration of an organized cardiac rhythm with heart rate [HR] greater than 100/min and mean arterial pressure [MAP] greater than 20 mm Hg). Fifteen minutes after ROSC, FIO_2 was decreased to 30%.

Intervention

After stabilization, animals were randomly assigned to one of the two following experimental groups (n = 12/group): 1) in the control (CTRL) group, animals underwent CA followed by 120 minutes of reperfusion with continuous IV infusion of normal saline (NaCl 0.9%) at a rate of 5 mL/kg/hr and 2) in the lactate-treated group (MSL group), animals underwent CA followed by 120 minutes of reperfusion with continuous IV infusion of MSL ("Etablissement pharmaceutique de l'APHP," Paris, France) at a rate of 5 mL/kg/hr for the 120 minutes of reperfusion. The dose was chosen because it was shown to be protective in experimental septic shock, whose pathophysiology is close to that of post-CA syndrome (3, 10, 11).

Measurements

As syringes filled with either saline or MSL were unlabeled (according to randomization), investigators were unaware of the intervention during the whole protocol.

To clinically assess brain stem injury, pupillary diameter (measured with a pupil gauge) and reactivity to light (defined as present when pupils constricted more than 1 mm) at baseline and at 120 minutes were recorded (19). In addition, serum S100β protein level, a validated biomarker of irreversible brain injury, was

determined using an enzyme-linked immunosorbent assay test (Abnova, Taipei, Taiwan). Survival was assessed at 120 minutes of reperfusion.

MAP, HR, $ETCO_2$, and temperature were continuously recorded. Left ventricular (LV) end-diastolic pressure (LVEDP) was measured at the end of the reperfusion period using a fluid filled catheter inserted through the apex of the LV.

Echocardiography (Vivid E95, GE medical system, Milwaukee, WI) was performed at baseline and 30, 60, and 120 minutes of reperfusion to measure LV surface shortening fraction (SSF) and cardiac output (CO).

Fluid balance at 120 minutes was calculated as the difference between diuresis and all fluid intakes.

Arterial blood gases were measured using ABL800 Flex (Radiometer Medical, Copenhagen, Denmark). Hematocrit was determined using a centrifugation method on a Hettich Haematokrit 210 (Hettich Laboratory, Golden Valley, MN). Centrifuged and frozen blood samples were assayed (e.g., electrolytes, creatinine, glucose, alanine aminotransferase [ALT], lactatemia, protidemia, troponin Ic, and osmolality) at an off-site reference laboratory blinded to clinical data.

Brain Mitochondria Function

At the end of the protocol, left cerebral cortex piece was harvested. Brain mitochondrial fractions were isolated by differential centrifugation, as previously described (19–22).

State 2 (adenosine diphosphate [ADP]-limited), state 3 (ADP-stimulated), and respiratory control index (RCI: state 3/state 2, a measure of mitochondrial coupling between oxygen consumption and adenosine triphosphate [ATP] production) were determined by oxygraphy (Oroboros Oxygraph 2-K, Oroboros Instrument, Graz, Austria) in the presence of electron donors to complex I (5-mM glutamate, malate, and pyruvate), as previously described (19–22).

Calcium retention capacity (CRC), a functional test for a quantitative assessment of the in vitro sensitivity of the mitochondrial permeability transition pore (mPTP) to calcium loading, was measured as previously described (19–22). Extramitochondrial Ca^{2+} concentration was determined using the calcium sensitive probe calcium green-5N (Molecular Probes, Eugene, OR). The amount of $CaCl_2$ necessary to trigger a massive Ca^{2+} release (i.e., CRC) was used here as an indicator of the susceptibility of mPTP opening.

Statistical Analysis

The sample size calculation (n = 12/group) was based on an anticipated increase in the proportion of animals with preserved pupillary reactivity at 120 minutes (primary endpoint) from 25% to 75% with treatment (power = 90%; α = 0.05). Data were expressed as mean ± SEM or count (percentage). Comparisons of categorical variables were performed using Fisher exact test, and continuous variables were compared using Student t test or Mann-Whitney U test, as appropriate. Comparisons between time-based measurements within each group were performed with two-way analysis of variance with repeated measures on one factor. Data were analyzed using Graphpad Prism 6 (GraphPad, La Jolla, CA). $p < 0.05$ was considered as statistically significant.

RESULTS

There was no significant difference in both the CA characteristics and the CPR parameters between the two groups (**Table 1**), as well as in the core temperature at baseline (38.6°C ± 0.3°C for CTRL group and 38.5°C ± 0.2°C for MSL group; $p > 0.05$), during CA, and throughout the reperfusion period. During CA, the mean systemic pressure was 4.8 ± 1.3 mm Hg for the CTRL group and 5.5 ± 0.5 mm Hg for the MSL group ($p > 0.99$). Survival did not significantly differ between the two groups (Table 1).

MSL Reduced Brain Injury and Improved Brain Mitochondria Functions

At the end of the protocol, the proportion of animals with pupillary reactivity was significantly ($p = 0.012$) higher in the MSL group (10/12, 83%) than that in the CTRL group (three of 12, 25%), whereas pupillary diameter was similar (**Table 2**). The CA-induced increase in S100β protein was significantly lower in the MSL group than that in the CTRL group (Table 2). ADP-stimulated oxygen consumption (state 3), RCI, and CRC were significantly higher in the MSL group than that in the CTRL group (Table 2).

MSL Improved Hemodynamic Status and Cardiac Performance

MAP, SSF, and CO were significantly lower 30 minutes after ROSC than the baseline in the two groups ($p < 0.05$

TABLE 1.
Cardiac Arrest, Resuscitation and Survival

Variables	Control Group	Molar Sodium Lactate Group	*p*
Asphyxia before cardiac arrest (s)	340 ± 13	343 ± 10	0.842
VF during CPR	2/12 (17)	1/12 (8)	> 0.999
CPR duration (s)	160 ± 43	120 ± 15	0.758
CPR duration in rabbits without VF (s)	106 ± 7	106 ± 10	0.956
Epinephrine (μg/kg)	15 ± 2	14 ± 1	0.629
Restoration of spontaneous circulation	11/12 (92)	12/12 (100)	1.000
Survival	9/12 (75)	10/12 (83)	> 0.999

CPR = cardiopulmonary resuscitation, VF = ventricular fibrillation.
Data are expressed as mean ± SEM or number (%).

TABLE 2.
Brain Injury at 120 Minutes of Reperfusion

Parameters	Control Group	Molar Sodium Lactate Group	*p*
Pupillary examination			
Pupillary diameter (mm)	7 ± 0	6 ± 0	0.471
Pupillary reactivity	3/12 (25%)	10/12 (83%)	0.012
Brain injury biomarker			
Serum S100β protein (pg/mL)	412 ± 63	189 ± 42	0.008
Brain mitochondria functions			
State 2	6.1 ± 1.0	6.7 ± 0.4	0.591
State 3	19.4 ± 4.3	67.6 ± 6.6	< 0.001
Respiratory control index (state 3/state 2)	3.0 ± 1.1	10.2 ± 2.4	< 0.01
Calcium retention capacity (nmol Ca^{2+}/mg protein)	80.0 ± 10.7	177.1 ± 22.4	< 0.01

Data are expressed as mean ± SEM or number (%).
States 2 and 3 are expressed as nanogram atoms of oxygen/min/mg proteins.

for all six comparisons). At the end of the protocol, these three parameters were significantly higher in the MSL group than that in the CTRL group (**Fig. 1**), and the diastolic arterial pressure was significantly higher in the MSL group (43 ± 3 mm Hg) than that in the CTRL group (23 ± 3 mm Hg; $p = 0.023$). At this time point, MSL-treated rabbits also exhibited significantly lower LVEDP (3 ± 1 mm Hg) than CTRL animals (8 ± 2 mm Hg; $p = 0.003$). Troponin levels were higher in the CTRL group (19 ± 8 μg/L) than that in the MSL group (8 ± 4 μg/L) without reaching statistical significance ($p = 0.301$).

MSL Had Significant Effects on Volume Status

At baseline, hematocrit was not different between the CTRL (51% ± 3%) and MSL groups (48% ± 1%, $p = 0.832$). Although fluid intake was similar in the two groups, diuresis was significantly lower in the CTRL group than that in the MSL group, resulting in a higher positive fluid balance in the CTRL group. Hematocrit and protidemia did not significantly differ at 120 minutes between the two groups (**Table 3**).

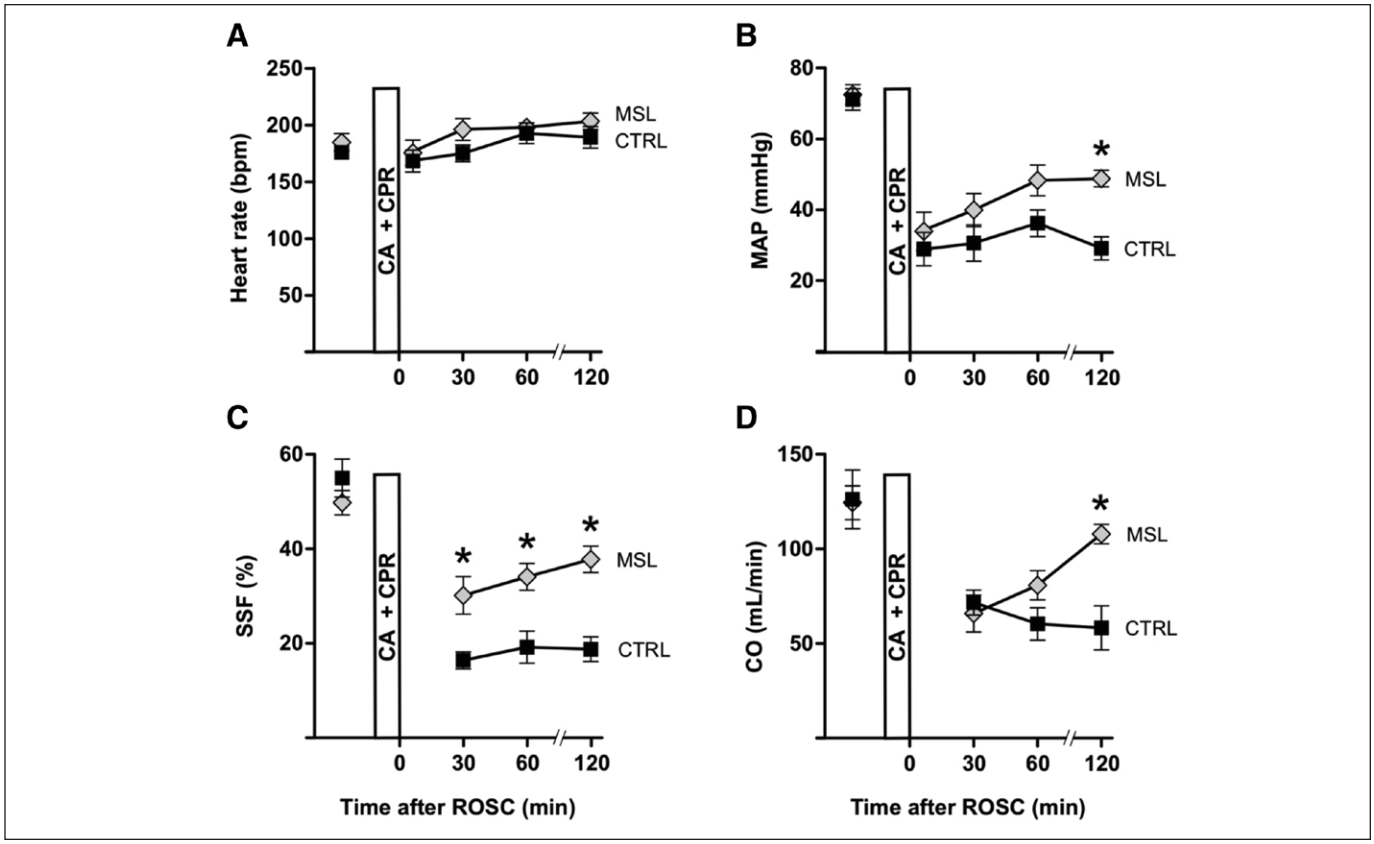

Figure 1. Effects of molar sodium lactate (MSL) on post-cardiac arrest (CA) shock. Heart rate (**A**), mean arterial pressure (MAP) (**B**), surface shortening fraction (SSF) (**C**), and cardiac output (CO) (**D**) are plotted at baseline, and at 5, 30, 60, and 120 min after restoration of spontaneous circulation (ROSC) for control (CTRL) animals (*black square*) and MSL)-treated rabbits (*gray diamond*). Data are represented as mean ± SEM; each group was composed of 12 animals. *$p < 0.05$ MSL vs CTRL (two-way analysis of variance for repeated measure). CPR = cardiopulmonary resuscitation.

TABLE 3.
Determinants and Markers of Volume Status at 120 Minutes of Reperfusion

Parameters	Control Group	Molar Sodium Lactate Group	*p*
Volemia determinants			
Fluid intake (mL/kg)	11.5 ± 0.2	11.4 ± 0.1	0.733
Diuresis (mL/kg)	2.3 ± 1.4	12.5 ± 2.5	0.014
Fluid balance (mL/kg)	11 ± 1	1 ± 3	0.014
Hemoconcentration markers			
Hematocrit (%)	39 ± 2	41 ± 2	0.215
Protidemia (g/L)	33 ± 2	35 ± 2	0.943

Data are expressed as mean ± SEM.

MSL Had Significant Effects on Metabolic Disorders

Arterial lactatemia significantly increased after CA in both groups and was significantly higher in the MSL group than that in the CTRL group throughout the reperfusion period (Supplemental Digital Content, **Fig. 1**, http://links.lww.com/CCM/G670). At 120 minutes of reperfusion, despite a significantly higher lactatemia in the MSL group, pH tended to be higher, and bicarbonate level was significantly higher than that in CTRLs (**Table 4**). Na^+ level was significantly higher in

TABLE 4.
Metabolic Disorders and Organ Injury Markers at 120 Minutes of Reperfusion

Blood Biochemistry Data	Control Group	Molar Sodium Lactate Group	*p*
Lactate (mmol/L)	15.0 ± 2.2	27.7 ± 4.3	0.018
Na^+ (mmol/L)	143 ± 6	157 ± 2	0.008
K^+ (mmol/L)	9 ± 1	6 ± 1	< 0.001
Cl^- (mmol/L)	101 ± 2	94 ± 1	0.010
HCO_3^- (mmol/L)	9 ± 3	21 ± 3	0.001
pH	7.14 ± 0.05	7.31 ± 0.06	0.071
Osmolality (mOsm/kg)	360 ± 14	347 ± 6	0.357
Osmolarity (mOsm/kg)[a]	348 ± 12	352 ± 3	0.681
Glucose (mmol/L)	35 ± 1	25 ± 2	0.003
Creatinine (μmol/L)	144 ± 6	125 ± 7	0.090
Alanine aminotransferase (international units/L)	97 ± 22	59 ± 12	0.112

[a]Osmolarity was calculated as follows: $1.86 \times (Na^{2+} \times K^+) + 1.15 \times$ glucose + urea + 14.
Data are expressed as mean ± SEM.

the MSL group than that in the CTRL group, and K^+ level was significantly lower in the MSL group than the CTRL group (Table 4). There was a trend toward less liver and kidney injury in MSL-treated rabbits compared with CTRL animals as evidence by lower ALT and creatinine levels, respectively (Table 4).

DISCUSSION

The present study demonstrated that continuous MSL infusion after ROSC is effective in limiting CA-induced neurologic injury and cardiovascular dysfunction, the two main components of the post-CA syndrome, in a rabbit model of primary asphyxial CA. These protective effects were associated with an improvement in fluid balance, acid-base status, and brain mitochondria functions.

Irreversible brain injury is responsible for the majority of deaths after CA (3), making brain injury a priority therapeutic target. In the present study, MSL administration resulted in lower brain stem injury, as suggested by the higher proportion of rabbits with reactive pupils in the MSL group compared with the CLTR group at the end of the protocol. Pupillary light reflex is indeed one of the most powerful clinical parameters for predicting neurologic prognosis after post-CA coma, even at a very early phase and irrespective of temperature and sedation (24). Serum S100β protein level, a marker of astrocytes lysis and a potent predictor of outcome after CA (24), was also significantly lowered after MSL infusion, further confirming MSL-induced neuroprotection. In agreement with these findings, it has been previously shown in patients with traumatic brain injury that administration of hypertonic sodium lactate prevented raise in intracranial pressure, and improved cerebral perfusion and neurologic outcomes, independently of any hyperosmolar effect (15, 25). These neuroprotective effects may be related to the fact that lactate is a better substrate than glucose in vitro and in vivo for ischemic neurons (18, 26). Indeed, unlike glucose, lactate diffuses freely through cell membranes and does not require ATP-dependent activation via phosphorylation to enter the glycolysis pathway (27). In other words, lactate is readily oxidizable, which is an obvious advantage in contexts of energy crisis.

A possible explanation for MSL-induced neuroprotection is an improvement in brain mitochondria functions, which are essential organelles for cell homeostasis and lactate metabolism, especially in energy crisis settings. These organelles synthesize ATP, and regulate cell calcium homeostasis and cell death (28). We and others have previously highlighted the key role of mPTP opening (a mega-canal located in the inner membrane of mitochondria) in the pathophysiology of the post-CA syndrome (19–22, 29, 30). Indeed, under stress

conditions (e.g., burst of reactive oxygen species and calcium overload), mPTP opening drives the uncoupling of the respiratory chain, mitochondrial matrix swelling, and efflux proapoptotic factors (28). Here, we found that MSL infusion was associated with both an increase in CRC indicating lower susceptibility to deleterious mPTP opening and an improvement in oxidative phosphorylation (i.e., increase in ADP-stimulated respiration). To our knowledge, the effects of hypertonic sodium lactate on mitochondrial function in the context of brain energy crisis have only been investigated in a model of traumatic brain injury (13). In agreement with the results presented herein, the authors have found a significant improvement in both mitochondrial respiration and preservation of mitochondrial ultrastructure, which suggests that the mPTP remained in a closed conformation. Nevertheless, whether MSL has direct or indirect effects on the preservation of mitochondrial functions remains to be determined.

In clinical practice, post-CA shock occurs in almost 70% of CA patients and accounts for one-third of deaths among these patients (3). It is characterized by decreased ejection fraction, low CO, and vasoplegia combined with endothelial dysfunction (4). In the present study, MSL improved recovery from CA-induced impairment in hemodynamics. Thus, CO was almost normalized to baseline values at 120 minutes of reperfusion in the MSL group, whereas it remained severely decreased in the CTRL group. This result is unlikely to be due to higher HR or volemia in the MSL group. Indeed, a similar hemodilution (estimated by hematocrit and protidemia) at 120 minutes was observed despite very different fluid balances, suggesting that volemia was similar in the two groups. The increase in CO was therefore more likely related to an improved inotropism; this hypothesis is supported by the higher SSF found in the MSL group during the whole reperfusion period. The improvement in systolic function observed herein is in line with both clinical (13–15) and experimental studies (10, 31, 32), where it has been attributed to an intrinsic effect of lactate as energetic substrate (17, 31–33). Interestingly, LVEDP was significantly lower at the end of the protocol in the MSL group than CTRLs, suggesting that MSL may also prevent CA-induced diastolic dysfunction, which might be an independent factor for poor survival in this setting (34). In agreement with the findings presented herein, a previous study has found a significant improvement in diastolic function after lactate sodium infusion in a porcine model of septic shock (11).

Along with cardiac dysfunction, vasoplegia is a major component of the post-CA shock (4). In the present study, MAP was higher in the MSL-treated rabbits than that in the CTRL animals. This finding could be explained by the potential benefits of MSL on vascular tone, as suggested by the higher diastolic arterial pressure in the MSL-treated rabbits, in addition to the higher CO. Furthermore, because cumulative fluid balance was much higher in the CTRL group than that in the MSL group, without any difference in hemodilution, one could reasonably assume that capillary leakage due to endothelial dysfunction was more pronounced in CTRL animals. This hypothesis is supported by previous studies that have reported an association between the use of MSL and the preservation of endothelial function in experimental sepsis (10, 32) or in pediatric septic shock (16). In addition, higher pH in the MSL group might have improved vascular reactivity to endogenous vasopressors.

The present study has some limitations. First, the duration of observation was limited to 120 minutes, so it cannot be ruled out that the intervention only delayed tissue damage, especially irreversible brain injury. Second, MSL was not compared with another iso-osmolar fluid with alkalinizing effect such as molar sodium bicarbonate. Nevertheless, as sodium bicarbonate is not recommended for CPR because of a lack of benefits (3), it was not the best comparator in a preclinical study. Furthermore, previous studies reported that bicarbonate was inferior to MSL for improving outcomes in experimental shock (11, 32). In addition, we did not compare MSL to hypertonic saline. Nevertheless, osmolarity was similar between the two groups, suggesting that the benefits of MSL were not related to hypertonicity. Furthermore, hypertonic saline has already been investigated in CA and failed to improve outcomes (35). Third, only one modality of use of MSL among many (6–17, 31–33) was investigated. We cannot therefore rule out that other doses and/or durations of administration may lead to better results and/or less side effects.

CONCLUSIONS

The present study showed that continuous MSL infusion at reperfusion reduced the severity of post-CA syndrome. Clinical trials are now required to

determine whether these experimental results can be translated into humans.

ACKNOWLEDGMENTS

We thank Dr. Boyer (Direction de la Recherche Clinique et de l'Innovation, Hospices Civils de Lyon) for her help in article preparation (funding: Hospices Civils de Lyon).

1 *Université de Lyon, INSERM UMR1060 (CarMeN), IRIS, Lyon, France.*

2 *Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive-Réanimation, Lyon, France.*

3 *Service de Biochimie et Biologie Moléculaire Grand Est, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, France.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by a research grant from the "ALLP Groupe ADENE."

The work was performed at Université de Lyon, INSERM UMR1060 (CarMeN), IRIS team, Lyon, France.

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: martin.cour@chu-lyon.fr

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics-2020 update: A report from the American Heart Association. *Circulation* 2020; 141:e139–e596
2. Gräsner JT, Wnent J, Herlitz J, et al: Survival after out-of-hospital cardiac arrest in Europe - results of the EuReCa TWO study. *Resuscitation* 2020; 148:218–226
3. Neumar RW, Nolan JP, Adrie C, et al: ILCOR consensus statement post-cardiac arrest syndrome epidemiology, pathophysiology, treatment, and pognostication. *Circulation* 2008; 118:2452–2483
4. Lemiale V, Dumas F, Mongardon N, et al: Intensive care unit mortality after cardiac arrest: The relative contribution of shock and brain injury in a large cohort. *Intensive Care Med* 2013; 39:1972–1980
5. Kirkegaard H, Taccone FS, Skrifvars M, et al: Postresuscitation care after out-of-hospital cardiac arrest: Clinical update and focus on targeted temperature management. *Anesthesiology* 2019; 131:186–208
6. Kulling PE: Treatment of cardiac membrane stabilizing dysrhythmias. *J Toxicol Clin Toxicol* 1996; 34:131–134
7. Bellet S, Wasserman F, Brody JI: Molar sodium lactate; its effect in complete atrioventricular heart block and cardiac arrest occurring during Stokes-Adams seizures and in the terminal state. *N Engl J Med* 1955; 253:891–900
8. Bellet S, Wasserman F, Brody JI: Treatment of cardiac arrest and slow ventricular rates in complete A-V heart block; use of molar and half molar sodium lactate: A clinical study. *Circulation* 1955; 11:685–701
9. Silverman LM, Eichert H: Molar sodium lactate compared with electrical stimulation in cardiac arrest. *J Am Med Assoc* 1957; 164:1209–1211
10. 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
11. Duburcq T, Durand A, Tournoys A, et al: Sodium lactate improves renal microvascular thrombosis compared to sodium bicarbonate and 0.9% NaCl in a porcine model of endotoxic shock: An experimental randomized open label controlled study. *Ann Intensive Care* 2018; 8:24
12. 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
13. 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; 34:1796–1803
14. Nalos M, Leverve XM, 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; 18:48
15. 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; 35:471–479
16. Millet A, Cuisinier A, Bouzat P, et al: Hypertonic sodium lactate reverses brain oxygenation and metabolism dysfunction after traumatic brain injury. *Br J Anaesth* 2018; 120:1295–1303
17. Fontaine E, Orban JC, Ichai C: Hyperosmolar sodium-lactate in the ICU: Vascular filling and cellular feeding. *Crit Care* 2014; 18:599
18. Gallagher CN, Carpenter KL, Grice P, et al: The human brain utilizes lactate via the tricarboxylic acid cycle: A 13C-labelled microdialysis and high-resolution nuclear magnetic resonance study. *Brain* 2009; 132:2839–2849
19. Cour M, Loufouat J, Paillard M, et al: Inhibition of mitochondrial permeability transition to prevent the post-cardiac arrest syndrome: A pre-clinical study. *Eur Heart J* 2011; 32:226–235
20. Cour M, Jahandiez V, Loufouat J, et al: Minor changes in core temperature prior to cardiac arrest influence outcomes: An experimental study. *J Cardiovasc Pharmacol Ther* 2015; 20:407–413
21. Jahandiez V, Cour M, Bochaton T, et al: Fast therapeutic hypothermia prevents post-cardiac arrest syndrome through cyclophilin D-mediated mitochondrial permeability transition inhibition. *Basic Res Cardiol* 2017; 112:35
22. Jahandiez V, Cour M, Abrial M, et al: Therapeutic hypothermia after cardiac arrest: Involvement of the risk pathway in mitochondrial PTP-mediated neuroprotection. *Shock* 2019; 52:224–229

23. Uthamanthil RK, Hachem RY, Gagea M, et al: Urinary catheterization of male rabbits: A new technique and a review of urogenital anatomy. *J Am Assoc Lab Anim Sci* 2013; 52:180–185
24. Rossetti AO, Rabinstein AA, Oddo M: Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol* 2016; 15:597–609
25. Carteron L, Solari D, Patet C, et al: Hypertonic lactate to improve cerebral perfusion and glucose availability after acute brain injury. *Crit Care Med* 2018; 46:1649–1655
26. Schurr A, Payne RS, Miller JJ, et al: Brain lactate, not glucose, fuels the recovery of synaptic function from hypoxia upon reoxygenation: An *in vitro* study. *Brain Res* 1997; 744:105–111
27. Halestrap AP, Wilson MC: The monocarboxylate transporter family–role and regulation. *IUBMB Life* 2012; 64:109–119
28. Cour M, Gomez L, Mewton N, et al: Postconditioning: From the bench to bedside. *J Cardiovasc Pharmacol Ther* 2011; 16:117–130
29. Argaud L, Cour M, Dubien PY, et al; CYRUS Study Group: Effect of cyclosporine in nonshockable out-of-hospital cardiac arrest: The CYRUS randomized clinical trial. *JAMA Cardiol* 2016; 1:557–565
30. Kreitmann L, Argaud L, Ovize M, et al; CYRUS Study Group: Cyclosporine A prevents cardiac arrest-induced acute respiratory failure: A post-hoc analysis of the CYRUS trial. *Intensive Care Med* 2020; 46:1281–1283
31. Kline JA, Thornton LR, Lopaschuk GD, et al: Lactate improves cardiac efficiency after hemorrhagic shock. *Shock* 2000; 14:215–221
32. Besnier E, Coquerel D, Kouadri G, et al: Hypertonic sodium lactate improves microcirculation, cardiac function, and inflammation in a rat model of sepsis. *Crit Care* 2020; 24:354
33. Levy B, Mansart A, Montemont C, et al: Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock. *Intensive Care Med* 2007; 33:495–502
34. Jentzer JC, Chonde MD, Dezfulian C: Myocardial dysfunction and shock after cardiac arrest. *Biomed Res Int* 2015; 2015:314796
35. Breil M, Krep H, Heister U, et al: Randomised study of hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest. *Resuscitation* 2012; 83:347–352