ORIGINAL ARTICLE

Vol. 10 No. 1 January-March 2025

doi: 10.35366/118935

Hepatotoxic effects of lactated Ringer's solution in patients undergoing cardiac surgery at a national referral center

Efectos hepatotóxicos del lactato de Ringer en pacientes sometidos a cirugía cardiaca en un centro de referencia nacional

Yoana Leyva-López,* Frida Rivera-Buendía,‡ Diego B. Ortega-Zhindón§

* Department of Clinical Research.
‡ London School of Hygiene and Tropical Medicine. London, United Kingdom.
§ Department of Pediatric Cardiac Surgery and Congenital Heart Disease; Instituto Nacional de Cardiología Ignacio Chávez. Mexico City, México.

ABSTRACT

Objective: we describe a case series of twelve patients who underwent cardiac surgery that developed acute hepatic failure (AHF) following the administration of Lactated Ringer's solution (LRS). **Material and methods:** an observational and retrospective study was carried out. Patients diagnosed with AHF undergoing cardiac surgery from January 1, 2018 and December 31, 2018, were included; perioperative characteristics and conditions were considered. **Results:** these patients received a mean of 100 ml/h of LRS for a hypovolemic replacement over about 3.8 ± 2.7 days. AHF and hepatocellular damage pattern, was confirmed in twelve patients and is potentially associated with drug-induced liver injury (DILI) due to LRS. At follow-up, four patients were discharged from the hospital, while eight died during hospital stay. **Conclusions:** carefully assessing lactic acid levels and liver enzymes in cardiac surgery patients during their intensive care unit stay before starting infusion with LRS is important. The prevention of hyperlactatemia complications requires an initial assessment of lactate metabolism.

Keywords: hepatotoxic activity, lactated Ringer's solution, acute hepatic failure, cardiac surgery.

RESUMEN

Objetivo: *describimos una serie de casos de doce pacientes sometidos a cirugía cardiaca que desarrollaron insuficiencia hepática aguda (IHA) tras la administración de lactato de Ringer (LR).* ***Material y métodos:*** *se realizó un estudio observacional y retrospectivo. Se incluyeron pacientes diagnosticados de IHA sometidos a cirugía cardiaca entre el 01 de enero de 2018 y el 31 de diciembre de 2018; se consideraron las características y condiciones perioperatorias.* ***Resultados:*** *estos pacientes recibieron un promedio de 100 ml/h de LR para un reemplazo durante aproximadamente 3.8 ± 2.7 días. En doce pacientes se confirmó IHA y un patrón de daño hepatocelular, potencialmente asociado a la lesión hepática inducida por fármacos (LHIF) debido a LR. Durante el seguimiento, cuatro pacientes recibieron el alta hospitalaria, mientras que ocho fallecieron durante su estancia en el hospital.* ***Conclusiones:*** *la evaluación cuidadosa de los niveles de ácido láctico y enzimas hepáticas en pacientes de cirugía cardíaca durante su estancia en la unidad de cuidados intensivos antes de iniciar la infusión con LR es importante. La prevención de complicaciones por hiperlactatemia requiere una evaluación inicial del metabolismo del lactato.*

Palabras clave: *hepatotoxicidad, solución de lactato de Ringer, insuficiencia hepática aguda, cirugía cardiaca.*

How to cite: Leyva-López Y, Rivera-Buendía F, Ortega-Zhindón DB. Hepatotoxic effects of lactated Ringer's solution in patients undergoing cardiac surgery at a national referral center. Cir Card Mex. 2025; 10 (1): 5-13. https://dx.doi.org/10.35366/118935

Received: 10-20-2024. Accepted: 11-01-2024.

Correspondence: Dr. Diego B. Ortega-Zhindón, E-mail: diegob.ortegaz@gmail.com

Abbreviatures:
AHF = acute hepatic failure
AKI = acute kidney injury
ALP = alkaline phosphatase
ALT = alanine aminotransferase
AST = aspartate aminotransferase
AVR = aortic valve replacement
DILI = drug-induced liver injury
ICU = intensive care unit
LDH = lactate dehydrogenase
LRS = lactated Ringer's solution
MVR = mitral valve replacement
pCO_2 = partial pressure of carbon dioxide
RUCAM = Roussel Uclaf causality assessment method
ULN = upper limit of normal

Patients who have undergone cardiac surgery, large volumes of crystalloid solutions, such as lactated Ringer's solution (LRS), are commonly administered to mitigate the effects of decreased tissue perfusion. The recommended dose of LRS ranged from 500 to 3,000 ml every 24 hours. Administration rates are adjusted based on the patient's clinical status, usually not exceeding 5 ml/kg/h.[1] However, using LRS could exacerbate basal serum lactate levels in some patients, leading to micro vascular and macrovascular circulation changes, a systemic inflammatory response, and subsequent organ damage. Particularly, hyperlactatemia could result in diffuse liver damage, characterized by a rapid and marked elevation of serum aminotransferases.[2] The prolonged exposure to hyperlactatemia may cause cellular and systemic dysfunction, resulting in severe metabolic acidosis, and in some cases, death. Although a relative increase in serum lactate levels is a common finding after cardiac surgery, the administration of LRS might drive the onset of severe hyperlactatemia and eventually, acute liver failure as a rare complication during the postoperative period.[3,4]

In this study, we describe a series of twelve cases who underwent cardiac surgery and further developed acute hepatic failure (AHF) during their intensive care unit (ICU) stay after receiving LRS as the initial replacement fluid therapy.

MATERIAL AND METHODS

We conducted a case series study of twelve patients undergoing cardiac surgery at the Instituto Nacional de Cardiología Ignacio Chávez from January 01, 2018 and December 31, 2018. We collected information on demographics, comorbidities, diagnoses, invasive procedures, biochemical parameters of liver function, and acid-base parameters of arterial gases (hydrogen potential (pH), partial pressure of carbon dioxide (pCO_2), bicarbonate (HCO_3^-), and serum lactate) during the first seven days of ICU stay. We determined whether there was an acid-base disturbance (metabolic acidosis, respiratory alkalosis, or mixed alkalosis).[5] AHF was defined according to the following: elevation of alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or alkaline phosphatase (ALP) > 2 times the ULN. Pattern of liver damage was defined as hepatocellular if the ULN of ALT or aspartate aminotransferase (AST) was greater than 5, cholestatic if there was a predominant elevation of ALP, and mixed if there was a combination of both.[6] We used the Roussel Uclaf causality assessment method (RUCAM) to determine the presence of drug-induced liver injury (DILI). Clinical outcomes included mortality or hospital discharge; additionally, we analyzed the relationship between acid-base disturbance, altered lactate metabolism, LRS administration, and acute liver injury. The IRB approved the study (INCAR-DG-DI-DI-CI-053-2023), adhering to the Declaration of Helsinki and following the CARE guidelines.

Data was collected using the REDCap electronic software (Vanderbilt University, Nashville, Tenn).[7] Continuous variables were presented as mean (± standard deviation) or median (interquartile range) according to the Anderson-Darling normality test. Categorical variables were presented as frequency and absolute proportion. Plots to visualize the changes in biochemical parameters and follow-up status were built with the ggplot2 R package.[8] We conducted all statistical analyses using R Studio version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Sociodemographic and clinical profile

Table 1 displays the sociodemographic and clinical characteristics at admission. The age ranged between 19 and 76, with a mean of 44.9 ± 16.8 years. Women made up 58% (n = 7) of the sample. The most common comorbidities were systemic arterial hypertension (33.3%, n = 5), type 2 diabetes mellitus (16.6%, n = 2), and chronic kidney disease (16.6%, n = 2). The admission diagnoses included one patient with acute aortic dissection type Stanford A and two with mitral regurgitation. Other diagnoses are shown in *Table 2*.

Cardiac surgery evaluation

Aortic valve replacement (AVR) and mitral valve replacement (MVR) were performed in six patients (50%), while Bentall-De Bono procedure was conducted in two patients (16.6%) *(Table 1)*. The twelve underwent cardiac surgery using cardiopulmonary bypass (CPB). The mean CPB time was 194 ± 68 minutes, aortic cross-clamping was 129 ± 35 minutes, temperature was 28 ± 4 °C, and the operative bleeding was 718 ± 386 ml.

Clinical condition

Table 2 shows patients' clinical findings during hospitalization. After the cardiac surgery, all patients were transferred to the ICU with normal hepatic function parameters. All patients received a mean dose of 100 ml per hour of LRS for hypovolemic replacement with a mean duration of 3.8 ± 2.7 days. During the first seven days of ICU stay, we observed clinical manifestations of increased lactate levels, lactic dehydrogenase, and clinical and laboratory evidence of hepatic damage (increase in the ALT/AST ratio) *(Figure 1)*. Postoperative metabolic acidosis was observed in seven patients (58.3%) and metabolic acidosis/mixed in five (41.6%) patients, which confirmed the clinical pattern of lactate metabolism deterioration. We observed confirmed acute hepatic failure in twelve patients (91.6%) due to marked elevation of ALT/AST greater than 5 ULN.

Table 1: Overall patient characteristics (N = 12).

Characteristics	Total n (%)
Female	7 (58)
Age (years)	44.9 ± 16.8
Body mass index (kg/m^2)	24.6 ± 3.6
NYHA class	
I	2 (16.6)
II	5 (41.6)
III	4 (33.3)
IV	1 (8.5)
Comorbidities	
Systemic arterial hypertension	5 (33.3)
Type 2 diabetes mellitus	2 (16.6)
Chronic kidney disease	2 (16.6)
Dyslipidemia	1 (8.3)
Smoking	3 (25)
Alcoholism	2 (16.6)
Cardiac surgery type	
Aortic valve replacement	3 (25)
Mitral valve replacement	3 (25)
Bentall-De Bono procedure	2 (16.6)
Others	4 (33.3)
Surgery characteristics	
CPB (min)	194 ± 68
Aortic cross-clamp (min)	129 ± 35
CPB Temperature (°C)	28 ± 4
Operative bleeding (ml)	718 ± 386
Biochemical evaluation	
pH (−log[H+])	7.3 ± 3.3
pCO2 (mmHg)	32 ± 5.4
HCO3− (mmol/l)	22.4 ± 4.0
Serum lactate (mmol/l)	1.3 ± 0.25
LDH (U/l)	151.5 ± 60.2
AST (U/l)	25.6 ± 10.7
ALT (U/l)	41.7 ± 43.7
Outcomes	
Length of hospital stay (days), median (IQR)	9 (IQR: 2.5-22.3)
Mortality	8 (66.7)

ALT = alanine aminotransferase. AST = aspartate aminotransferase. CPB = cardiopulmonary bypass. IQR = interquartile range. LDH = lactate dehydrogenase. NYHA = New York Heart Association.

Early outcomes

The median length of hospital stay was 9 (IQR:2.5-22.5) days. Four patients were discharged by clinical improvement, while eight died during hospitalization. The main causes of death were AHF (25%, n = 2), cardiogenic shock (37.5%, n = 3), septic shock (25%, n = 2), and mixed shock (12.5%, n = 1) *(Table 2 and Figure 1)*.

DISCUSSION

This case series evidenced that among 12 patients who were treated with LRS, 12 developed AHF and subsequently 8 died. Acute liver failure is feared complication in the ICU; DILI is diagnosed through the exclusion of other potential liver conditions and confirmed by relating potentially hepatotoxic substances to alterations in the liver's biochemical profile.[9] The increase in liver enzymes and temporal relationship with drug intake are the hallmark indicators of DILI, as there is currently no secure and accurate method for diagnosing it.[10] The most common type of DILI is hepatocellular, accounting for 52-75% of cases and characterized by a significant rise in ALT and/or AST concentrations due to drug administration.[10]

Exposure of hepatocytes to stress, most likely involving reactive metabolites, mitochondrial dysfunction, and oxidative stress, is believed to trigger DILI.[11] Inhibition of cytoplasmic (glycolysis) or mitochondrial (Krebs's cycle, oxidative phosphorylation) pathways leads to inadequate ATP production despite adequate amounts of oxygen and glucose, resulting in pyruvate and lactate accumulation under aerobic conditions, a situation known as cytotoxic hypoxia.[12] Histologic risk reduction and hypoxia impact the enzymatic pathways of pyruvate and lactate metabolism by stimulating anaerobic glycolysis and altering mitochondrial function, reducing lactate utilization and clearance. When the mitochondrial oxidative chain fails to generate NAD^+, pyruvate is reduced to lactate to produce NAD^+ and hypoxia affects both lactate utilization pathways.[13] In this context, LRS contains 28 mEq of lactate per liter and is the only solution that undergoes normal cellular metabolism in the liver, responsible for 60% of lactate clearance. During its metabolism as part of the Cori cycle, lactate is transformed into pyruvate and then into HCO_3^-.[2] A decrease

Table 2: Acid-base alterations and liver function before and after of cardiac surgery.

Patient	Initial diagnosis	Cardiac surgery	Drugs during the surgery	Laboratories		Acid-Base Disorder	Postoperative liver injury (ALT/AST > 5 LSN)	Ringer's lactate solution dose (ml/h/day)	Clinical outcome
				Preoperative	Postoperative				
1	Infective endocarditis (aortic valve)	AVR (mechanical)	Vasopressin Norepinephrine Levosimendan Dobutamine Midazolam Fentanyl Fast insulin	Lactate ↕ pH ↕ pCO_2 ↕ HCO_3^- ↓ ALT ↑ AST ↕ LDH ↑	Lactate ↑ pH ↓ pCO_2 ↓ HCO_3^- ↓ ALT ↑* 4 AST ↑ LDH ↑	Metabolic and/or mixed acidosis	Hepatocellular (ALT ↑)	100 ml/h/1 day 60 ml/h/1 day 40 ml/h/2 days 10 ml/h/2 days	Improvement
2	Mixed aortic valve disease	AVR and MVR (mechanical)	Vasopressin Norepinephrine Levosimendan Dobutamine Fentanyl Midazolam FAST insulin Dexmedetomidine	Lactate ↕ pH ↕ pCO_2 ↕ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↓	Lactate ↑ pH ↓ pCO_2 ↓ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic and/or mixed acidosis	Hepatocellular (ALT ↑)	100 ml/h/4 days 5 ml/h/1 day	Acute liver failure
3	Mitral regurgitation	MVR (biological)	Norepinephrine Dobutamine Levosimendan Furosemide Fentanyl Midazolam	Lactate ↕ pH ↕ pCO_2 ↕ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↕ pCO_2 ↕ HCO_3^- ↓ High NA AST ↑ LDH ↑	Metabolic and/or mixed acidosis	Hepatocellular (ALT ↑)	60 ml/h/2 days	Cardiogenic shock
4	Tetralogy of Fallot	Correction with bovine pericardial patch	Norepinephrine Fentanyl Vasopressin Midazolam Amiodarone	Lactate ↕ pH ↓ pCO_2 ↕ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↓ pCO_2 ↓ HCO_3^- ↓ High NA AST ↑ LDH ↑	Metabolic and/or mixed acidosis	Hepatocellular (ALT ↑)	100 ml/h/1 day	Cardiogenic shock

Continues Table 2: Acid-base alterations and liver function before and after of cardiac surgery.

Patient	Initial diagnosis	Cardiac surgery	Drugs during the surgery	Laboratories		Acid-Base Disorder	Postoperative liver injury (ALT/AST > 5 LSN)	Ringer's lactate solution dose (ml/h/day)	Clinical outcome
				Preoperative	Postoperative				
5	Mitral stenosis	MVR (mechanical)	Vasopressin Norepinephrine Levosimendan Fentanyl Midazolam Milrinone	Lactate ↕ pH ↓ pCO_2 ↕ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↓ pCO_2 ↓ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (ALT ↑)	100 ml/h/1 day 50 ml/h/2 days	Acute liver failure
6	Acute aortic dissection (Stanford A)	Replacement of supracoronary aorta and aortic arch	Vasopressin Levosimendan Norepinephrine Dobutamine Fentanyl Midazolam	Lactate ↕ pH ↕ pCO_2 ↓ HCO_3^- ↓ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↓ pCO_2 ↑ HCO_3^- ↓ High NA AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (ALT ↑)	100 ml/h/1 day	Cardiogenic shock
7	Acute aortic dissection (Stanford A)	Bentall-De Bono procedure	Vasopressin Norepinephrine Levosimendan Morphine Dobutamine Fentanyl Midazolam	Lactate ↕ pH ↕ pCO_2 ↓ HCO_3^- ↕ ALT ↑ AST ↕ LDH × 1.1	Lactate ↑ pH ↓ pCO_2 ↕ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (AST ↑)	60 ml/h/1 day 100 ml/h/1 day	Septic shock (AKI and AHF)
8	Mixed aortic valve disease and mitral regurgitation	AVR and MVR (biological)	Vasopressin Norepinephrine Levosimendan Dobutamine Fentanyl Midazolam	Lactate ↕ pH ↕ pCO_2 ↕ HCO_3^- ↕ ALT ↓ AST ↕ LDH ↕	Lactate ↑ pH ↕ pCO_2 ↕ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (AST ↑)	100 ml/h/1 day 50 ml/h/2 days	Septic shock (AKI and AHF)

Continues Table 2: Acid-base alterations and liver function before and after of cardiac surgery.

Patient	Initial diagnosis	Cardiac surgery	Drugs during the surgery	Laboratories		Acid-Base Disorder	Postoperative liver injury (ALT/AST > 5 LSN)	Ringer's lactate solution dose (ml/h/day)	Clinical outcome
				Preoperative	Postoperative				
9	Aortic prosthetic dysfunction	AVR (mechanical)	Vasopressin Norepinephrine Dobutamine Fentanyl Milrinone Morphine	Lactate ↕ pH ↕ pCO_2 ↓ HCO_3^- ↓ High NA AST ↕ LDH ↑	Lactate ↑ pH ↓ pCO_2 ↑ HCO_3^- ↓ High NA AST ↑ LDH ↑	Metabolic and/or mixed acidosis	None	100 ml/h/1 day 30 ml/h/1 day 10 ml/h/5 days	Improvement
10	Myocardial infarction	Coronary artery bypass grafting	Vasopressin Norepinephrine Dobutamine Fentanyl Midazolam	Lactate ↕ pH ↕ pCO_2 ↓ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↓ pCO_2 ↕ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (ALT ↑)	300 ml/h/1 day 60 ml/h/1 day 10 ml/h/1 day 0 ml/h/4 days 80 ml/h/1 day 40 ml/h/1 day	Septic shock and multi-organ failure
11	Acute aortic dissection (Stanford B)	Bentall-De Bono procedure	Vasopressin Norepinephrine Levosimendan Fentanyl Midazolam FAST insulin	Lactate ↑ pH ↕ pCO_2 ↕ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↓ pCO_2 ↕ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (AST ↑)	100 ml/h/1 day 200 ml/h/2 days 20 ml/h/7 days	Improvement
12	Chronic pulmonary thromboembolism	Bilateral pulmonary thromboendarterectomy	Vasopressin Norepinephrine Levosimendan Dopamine Dexmedetomidine Dobutamine Fentanyl	Lactate ↕ pH ↕ pCO_2 ↕ HCO_3^- ↕ ALT ↕ AST ↕ LDH ↕	Lactate ↑ pH ↓ pCO_2 ↕ HCO_3^- ↓ ALT ↑ AST ↑ LDH ↑	Metabolic acidosis	Hepatocellular (AST ↑)	100 ml/h/1 day 40 ml/h/1 day	Improvement

↑ = Increased by 1 normal upper limit. ↓ = decreased by 1 normal upper limit. ↕ = normal values. AHF = acute hepatic failure. AKI = acute kidney injury. ALT = alanine aminotransferase. AST = aspartate aminotransferase. AVR = aortic valve replacement. LDH = lactate dehydrogenase. MVR = mitral valve replacement. pCO_2 = partial pressure of carbon dioxide.

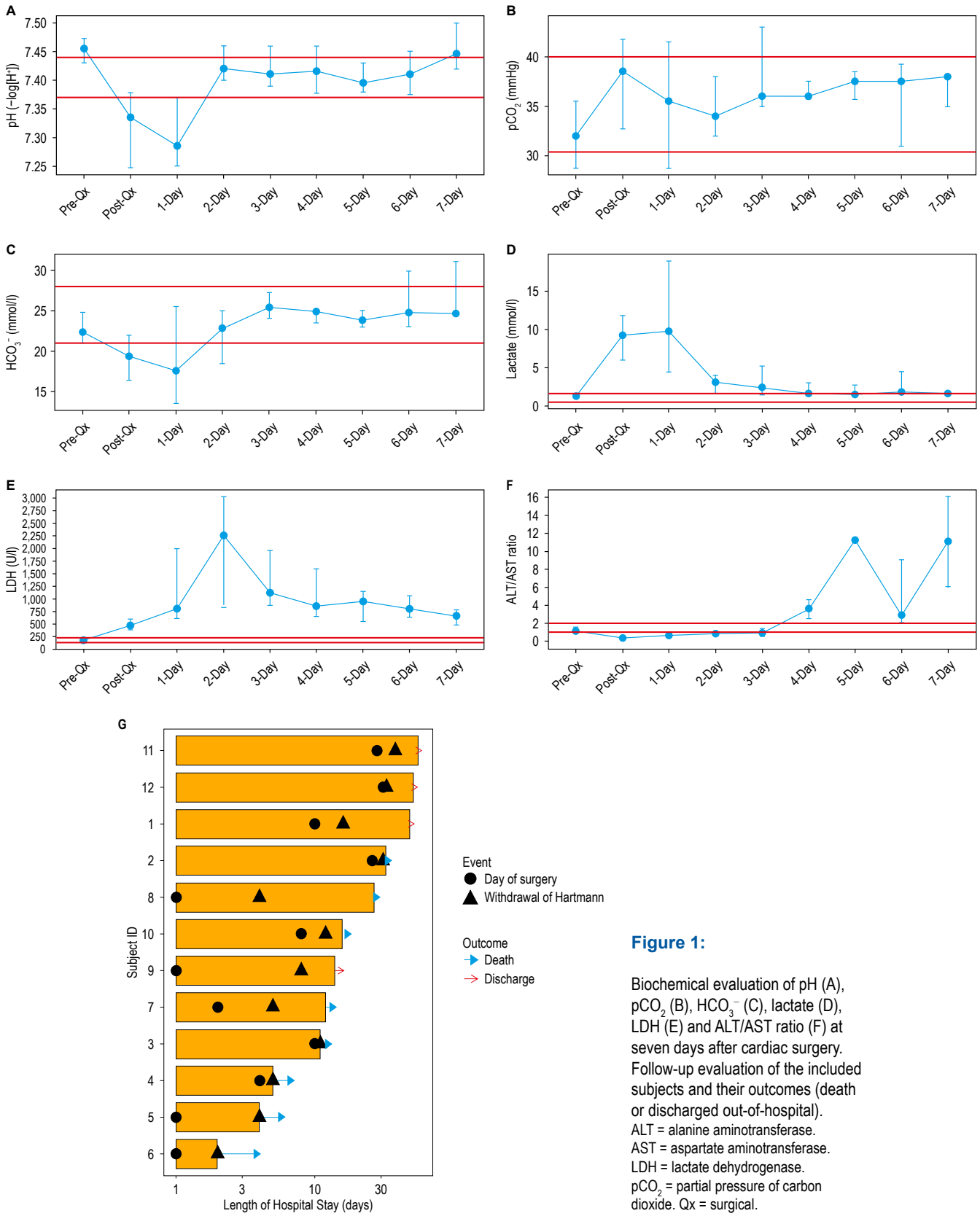

Figure 1:

Biochemical evaluation of pH (A), pCO_2 (B), HCO_3^- (C), lactate (D), LDH (E) and ALT/AST ratio (F) at seven days after cardiac surgery. Follow-up evaluation of the included subjects and their outcomes (death or discharged out-of-hospital).
ALT = alanine aminotransferase.
AST = aspartate aminotransferase.
LDH = lactate dehydrogenase.
pCO_2 = partial pressure of carbon dioxide. Qx = surgical.

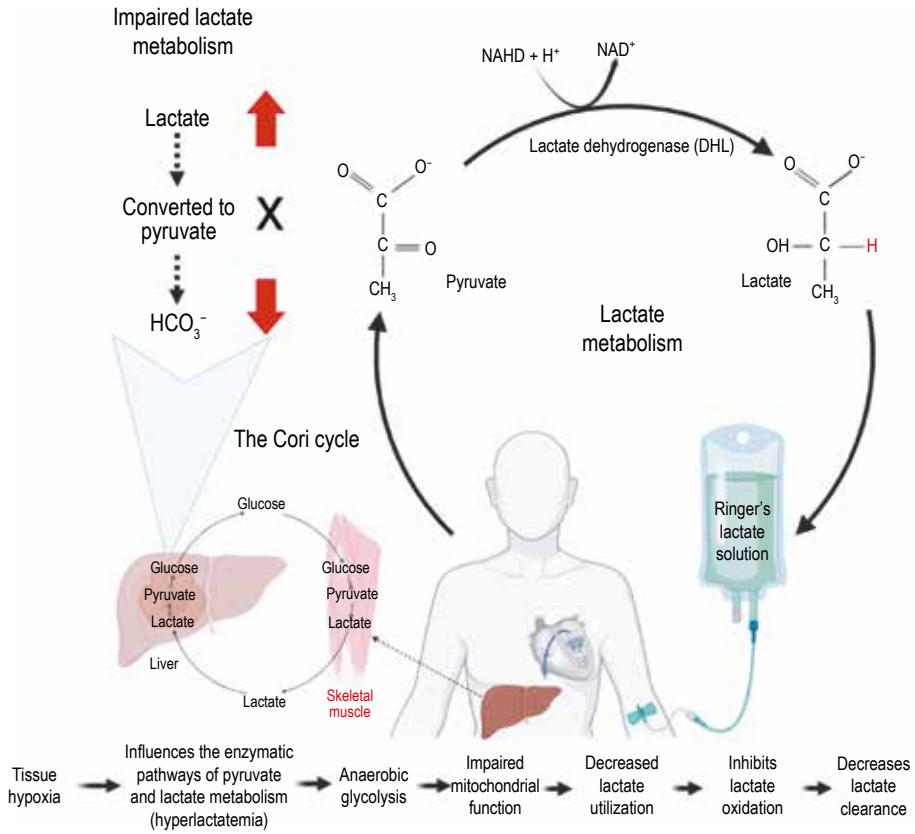

Figure 2:

Pathophysiological evaluation of lactate metabolism involved in acute hepatic failure.

in HCO_3^- and an increase in lactate indicate an alteration in lactate metabolism and excessive lactate administration beyond clearance can result in negative multiorgan effects. There is a theoretical possibility that administering large amounts of LRS could worsen existing lactic acidosis in septic shock and other states of peripheral hypoperfusion, which is further increased if there are bacterial infections and septic shock.[14,15] The potential relationship between serum lactate concentration and the dose of LRS administered with liver function alteration is shown in *Figure 2*, but further clinical studies are needed to confirm this relationship in septic shock and other states of peripheral hypoperfusion. Zitek et al., conducted a randomized clinical trial that examined the relationship between LRS administration and an increase in serum lactate levels, comparing healthy volunteers receiving LRS to those receiving saline solution at a dose of 30 ml/kg, the results showed that the mean lactate level increased from 1.06 to 1.99 mmol/l, corresponding to an increase of 0.93 mmol/L after LRS administration, though these results were not statistically significant.[14] Recently, another randomized clinical trial demonstrated that among patients undergoing cardiac surgery, the use of LRS did not reduce the risk of major adverse events over the following 90 days.[16] Currently, there is diverse ongoing clinical research regarding the use of crystalloid solutions and their impact on acid-base status, intra- and extracellular water content, plasma electrolyte compositions, and organ function. This study had important limitations, such as the fact that biochemical parameters of ALT/AST or ALP were not taken in all patients before, during, and after the invasive procedure. Another limitation is that currently, only the RUCAM method is available to evaluate the causality of DILI.

Overall, in clinical practice, it is important to look for all possible triggers of acute hepatic failure, to perform an initial analysis of the adequate function in lactate metabolism, before starting the infusion of lactate-containing crystalloids to avoid adverse clinical outcomes. As a last resort, in patients with acute hepatic failure with no evident cause, all medications or solutions that could be associated with this condition should be evaluated and suspended until the liver function or clinical status is resolved or restored.

CONCLUSIONS

These cases highlight the importance of addressing lactic acid and liver enzymes during the ICU stay of patients who underwent cardiac surgery before starting lactate-containing crystalloid infusion. An initial analysis of patients' lactate

metabolism function should be performed to prevent adverse clinical outcomes related to hyperlactatemia and its associated mechanisms. In cases where acute hepatic failure has been identified without an obvious cause, all medications or solutions that may be associated with this condition should be evaluated and suspended until liver function or clinical status is resolved or restored.

ACKNOWLEDGMENTS

We want to acknowledge the contribution of the Oficina de Apoyo Sistemático para la Investigación Superior (OASIS) of the Instituto Nacional de Cardiología Ignacio Chávez for the support for this manuscript.

Funding: none.

Conflict of interest: the authors have no conflicts of interest to disclose.

REFERENCES

1. Singh S, Kerndt CC, Davis D. "Ringer's lactate". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2023 Feb 28]. Available in: http://www.ncbi.nlm.nih.gov/books/NBK500033/
2. Katopodis P, Pappas EM, Katopodis KP. Acid-base abnormalities and liver dysfunction. Ann Hepatol. 2022;27(2):100675. doi: 10.1016/j.aohep.2022.100675.
3. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med. 2005;45(5):524-528. doi: 10.1016/j.annemergmed.2004.12.006.
4. Cardozo JDG, Yubero CRA, Okinaka YS. Lactate as a predictor of mortality in cardiovascular surgery. Rev Virtual Soc Parag Med Int. 2019;6(2):30-38. doi: 10.18004/rvspmi/2312-3893/2019.06.02.30-038.
5. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, Clinical Practice Guideline Panel: Chair:, Panel members, EASL Governing Board representative: EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222-1261. doi: 10.1016/j.jhep.2019.02.014.
6. Sandhu N, Navarro V. Drug-induced liver injury in GI practice. Hepatol Commun. 2020;4(5):631-645. doi: 10.1002/hep4.1503.
7. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208. doi: 10.1016/j.jbi.2019.103208.
8. Wickham H, Chang W, Henry L, et al. "ggplot2: Create elegant data visualisations using the grammar of graphics" [Internet]. 2023 [cited 2023 Feb 28]. Available in: https://CRAN.R-project.org/package=ggplot2
9. Weber S, Gerbes AL. Challenges and future of drug-induced liver injury research-laboratory tests. Int J Mol Sci. 2022;23(11):6049. doi: 10.3390/ijms23116049.
10. Andrade RJ, Chalasani N, Bjornsson ES, et al. Drug-induced liver injury. Nat Rev Dis Primer. 2019;5(1):58. doi: 10.1038/s41572-019-0105-0.
11. Bessone F, Hernandez N, Tagle M, et al. Drug-induced liver injury: a management position paper from the Latin American Association for Study of the liver. Ann Hepatol. 2021;24:100321. doi: 10.1016/j.aohep.2021.100321.
12. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate. Mayo Clin Proc. 2013;88(10):1127-1140. doi: 10.1016/j.mayocp.2013.06.012.
13. Li X, Yang Y, Zhang B, et al. Lactate metabolism in human health and disease. Signal Transduct Target Ther. 2022;7(1):305. doi: 10.1038/s41392-022-01151-3.
14. Zitek T, Skaggs ZD, Rahbar A, Patel J, Khan M. Does intravenous lactated Ringer's solution raise serum lactate? J Emerg Med. 2018;55(3):313-318. doi: 10.1016/j.jemermed.2018.05.031.
15. Strnad P, Tacke F, Koch A, Trautwein C. Liver-guardian, modifier and target of sepsis. Nat Rev Gastroenterol Hepatol. 2017;14(1):55-66. doi: 10.1038/nrgastro.2016.168.
16. Pesonen E, Vlasov H, Suojaranta R, et al. Effect of 4% albumin solution vs ringer acetate on major adverse events in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized clinical trial. JAMA. 2022;328(3):251-258. doi: 10.1001/jama.2022.10461.