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CLINICAL RESEARCH

Effects of intraoperative adrenergic administration on postoperative hyperlactatemia in open colon surgery: an observational study

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Abstract
Background: Postoperative Hyperlactatemia (PO-HL) is a frequent condition associated with poor prognosis. In recent years, there has been growing evidence that adrenergic stimulation may contribute to increased lactate levels. The use of adrenergic agonists for the control of intraoperative hypotension is frequent, and its impact on the development of PO-HL is unknown.
Objective: To evaluate whether the use of intraoperative adrenergic agents is associated with the occurrence of PO-HL.
Methods: This was a prospective observational study. The inclusion criteria were undergoing elective open colon surgery, being ≥60 years old and signing informed consent. The exclusion criteria were cognitive impairment, unplanned surgery, and anticipated need for postoperative mechanical ventilation. Baseline and intraoperative variables were collected, and arterial lactate data were collected at baseline and every 6 hours postoperatively for 24 hours. Hyperlactatemia was defined as lactate >2.1 mEq.L^{-1}.
Results: We studied 28 patients, 61% of whom developed hyperlactatemia. The variables associated with PO-HL in the univariate analysis were anesthetic time, the total dose of intraoperative ephedrine, and lower intraoperative central venous oxygen saturation ($ScvO_2$). Multivariate analysis confirmed the association between the use of ephedrine ($p = 0.004$), intraoperative hypotension ($p = 0.026$), and use of phenylephrine ($p = 0.001$) with PO-HL.

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Conclusions: The use of intraoperative ephedrine, phenylephrine and intraoperative hypotension were independently associated with the development of PO-HL. This finding should lead to new studies in this field, as well as a judicious interpretation of the finding of a postoperative increase in lactate levels.

Introduction

Postoperative Hyperlactatemia (PO-HL) is a common condition with a multifactorial origin that is associated with poor clinical outcomes in surgical patients.[1,2] PO-HL has been documented most extensively in patients recovering from cardiac or major abdominal surgery.[3–8]

Lactate has traditionally been viewed as a global marker of perfusion, as lactate levels increase when the oxygen demand exceeds supply.[9–13] Lactate is widely used for the diagnosis and management of shock conditions, and baseline measurement and follow-up are recommended to guide the initial resuscitation of critically ill patients.[14–17]

Recent findings have led to a re-evaluation of the role of lactate in organ metabolism during stress conditions, especially energy flow among compartments and systems.[18,19] Studies have also shed light on the mechanisms underlying the onset of hyperlactatemia.[18,20–22] For instance, elevated aerobic glycolysis, modulated by adrenergic stimulation, has been implicated in the process. This nonhypoxic lactate production is likely mediated by increased beta-2 activity and its ensuing effect on the Na^+/K^+-ATPase pump.[23–25]

Most studies on postoperative hyperlactatemia have focused on cardiac surgery. Two types of hyperlactatemia have been described in this population: type A, or early-onset, and type B, or late-onset. It has been reported that the use of adrenergic agonists such as adrenaline is associated with the onset of type B hyperlactatemia.[26–28]

Intraoperative hypotension is a frequent event that is associated with a higher risk of other complications, including cardiovascular events, cerebrovascular accidents, acute kidney injury, and even mortality.[29–31]

The objective of this study was to evaluate the association between the use of intraoperative adrenergic agents and the development of postoperative hyperlactatemia.

Methods

Design

Observational prospective cohort study. All patients who met the eligibility criteria were consecutively enrolled in this prospective cohort study. Patients were subjected to multimodal hemodynamic, perfusion, and cerebral oxygenation monitoring, as well as standard anesthetic and surgical protocols, as detailed below. Additional standardized information was collected from the medical records of enrolled patients. The reporting of this study was performed according to the Strobe Statement Guidelines for observational studies.

Setting

The study was carried out in the Operation Room (OR) and the Critical Care Unit of a university hospital between April 2010 and May 2013. All patients studied were followed up until hospital discharge.

Ethical aspects

The study was approved by the Scientific Ethics Committee of our institution, and all patients provided informed consent for participation.

Patients

Older adults subjected to elective open colorectal surgery were enrolled. The inclusion criteria were as follows: age ≥60 years old, agreement to undergo open colorectal surgery, and a signed informed consent form to participate in this study. The exclusion criteria were dementia evaluated based on a Mini-Mental State Examination (MMSE) <22, urgency or emergency surgery and a high risk for mechanical ventilation requirement before surgery. The patients enrolled in this study were part of a project designed to evaluate the association between perioperative perfusion and postoperative delirium; these results were recently published.[32] The patients were contacted by the research team once admitted to request their participation in the study, informed consent, baseline sampling, and registration of preoperative baseline characteristics. A secondary *a priori* objective of the project was to study perioperative perfusion disorders, specifically to evaluate the association between the evolution of postoperative perfusion parameters and hypotension and/or intraoperative interventions to manage hypotension (such as administration of fluids or vasoactive agents).

Patients were managed according to a standard surgical and anesthesia protocol, which is described below.

Baseline information

Preoperative data were collected, including demographic information, comorbidities, and stratification of preoperative anesthesia risk (ASA Physical Status Classification, American Society of Anesthesiologists). Blood samples were collected to measure baseline hemoglobin (ADVIA 2120, Siemens, Munich, Germany) and lactate levels (Vitros 5,1, Johnson & Johnson, New Jersey, US).

Anesthesia protocol

All patients were monitored with Electrocardiography (ECG), Pulse Oximetry (SpO_2), and continuous Mean Arterial Pressure (MAP) with an arterial line. After monitoring was initiated, an epidural catheter was inserted for postoperative analgesia. A sensor for monitoring the depth of anesthesia was applied and connected to a Bispectral Index (BIS™) monitor. A central venous catheter with continuous monitoring of Central Venous Oxygen Saturation ($ScvO_2$) was inserted (PreSep catheter and Vigileo™, Edwards Lifesciences®). Administration and monitoring of inhalation anesthesia were performed using an Aestiva 5 anesthesia machine (Datex-Ohmeda®, GE Healthcare).

Anesthesia induction was performed with a 2 $mg.kg^{-1}$ propofol IV bolus, Target-Controlled Infusion (TCI) of remifentanil, and 0.2 $mg.kg^{-1}$ cisatracurium IV bolus. In addition, patients were administered dexamethasone 4 mg IV, ondansetron 4 mg IV, ketoprofen 100 mg IV, and antibiotic prophylaxis with 1 g ceftriaxone IV plus 500 mg metronidazole IV. Hemodynamic parameters, $ScvO_2$, and BIS values were recorded every 5 minutes during anesthesia. The $ScvO_2$ measurements were masked to the attending anesthesiologist. Anesthesia maintenance was performed using 1% isoflurane and TCI remifentanil as needed, targeting BIS values of 45–65.

Ventilation and fluids were managed as previously reported. In the case of hypotension, pulse pressure variability was monitored to evaluate the need to administer an additional fluid bolus.[32] In the case of severe hypotension or hypotension unresponsive to fluids, vasopressors were administered according to the following protocol: in the absence of tachycardia, a 6–12 mg bolus of ephedrine was administered; if there was no response to ephedrine or if ephedrine was contraindicated, a 50–100 μg bolus of phenylephrine was administered. Finally, if there was no response to phenylephrine, norepinephrine infusion was initiated, targeting a MAP of 65–85 mmHg.

Before the surgery was completed, epidural analgesia was initiated with a solution of 0.1% bupivacaine plus 4 $\mu g.mL^{-1}$ fentanyl at an infusion rate of $5-8\ mL.h^{-1}$. Postoperative analgesia was performed by a team from the Anesthesiology Department.

Postoperative protocol

When the surgical procedure and anesthesia were complete, patients were transferred to the intermediate surgical unit of the Critical Care Unit for monitoring. Hemodynamic and perfusion parameters were recorded hourly, and arterial lactate was measured every 6 hours, until 24 hours of monitoring had been completed. If a patient developed hypotension, the fluid response was evaluated, and if there was no response, norepinephrine was initiated ($0.05\ \mu g.kg^{-1}.min^{-1}$). the patients were transferred to the basic ward at the discretion of the surgical team once the study measures were completed and were followed during their hospital stay by team members on a daily basis.

Definitions and cut-off points for variables of interest

The normal range for lactate was defined as 0.8–2.1 $mEq.L^{-1}$. Hyperlactatemia was defined as lactate >2.1 $mEq.L^{-1}$. Early-onset Hyperlactatemia (eHL) was defined as the presence of hyperlactatemia at the first measurement, 6 hours post-surgery,[28] and late-onset Hyperlactatemia (LHL) any lactate >2.1 $mEq.L^{-1}$ after the first measurement.

Statistical analysis and sample size

The sample size was calculated for the primary objective of this research project, as previously reported.[32] Baseline patient characteristics and intra- and postoperative measurements are expressed as a proportion or the mean ± SD. A chi-squared independence test, Fisher's exact test, or Student's *t*-test was used to evaluate associations between hyperlactatemia and baseline or intraoperative variables. A repeated measures ANOVA estimated by mixed models was used to evaluate associations between lactatemia at various time points and baseline or intraoperative variables; for this analysis, continuous variables were dichotomized according to the higher and lower values with respect to their medians. Given the likelihood of correlations among the various intraoperative variables potentially associated with hyperlactatemia, a multilevel mixed-effects linear regression analysis for repeated measures was developed to address our research question. Variables with *p*-values <0.25 in the univariate analysis were evaluated in the final model using the Hosmer and Lemeshow criteria.[33] A *p*-value < 0.05 was used to indicate significance in all analyses. Statistical analysis was performed using Stata 12.0 software (StataCorp LP, Texas, TX, USA, 2012), and figures were developed using GraphPad Prism 7.0 software.

Results

A total of 28 patients were studied between 2010 and 2013. The flowchart of evaluated patients is shown in Fig. 1. The average age was 73 ± 7 years, and 60.7% of patients were female. Indications for surgery were colon cancer (82.1%), colostomy reversal (14.3%), or other (3.6%). Regarding preoperative anesthesia risk, patients were classified as ASA I (35.7%) or ASA II (64.3%). Baseline blood values were hemoglobin 11 ± 2 $g.dL^{-1}$ and lactate 1.2 ± 0.3 $mEq.L^{-1}$.

In terms of hemodynamic parameters prior to anesthesia induction, the Mean Arterial Pressure (MAP) was 107 ± 16 mmHg, and the mean Systolic Arterial Pressure (SAP) was 157 ± 31 mmHg. During the intraoperative period, all patients had at least one episode of MAP below 65 mmHg, and 92.9% developed at least one episode of MAP below 60 mmHg. The mean intraoperative fluid intake was 1911 ± 985 mL. Of the total sample, 86% of patients received ephedrine (38 ± 27 mg), 57% received phenylephrine (493 ± 1172 mg), and 25% received norepinephrine (7 cases). The average time under anesthesia was 216 ± 64 minutes, and the average intraoperative $ScvO_2$ was 81%±8%. During the first day after surgery, 3 cases used NE at low doses (NE < $0.1\ \mu g.kg^{-1}.min^{-1}$).

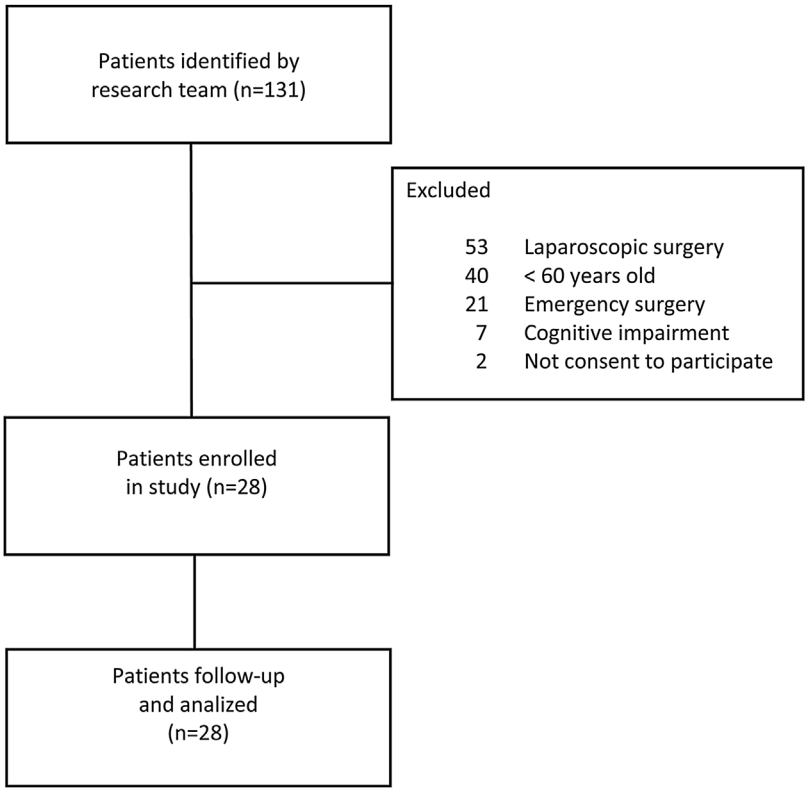

Figure 1 Flowchart of the study. Evaluated, excluded, and included patients.

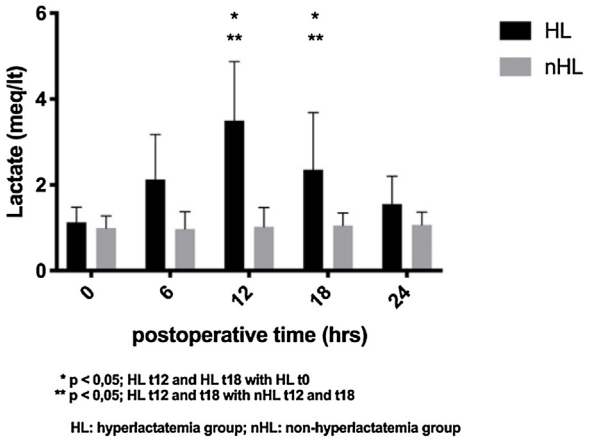

Figure 2 Postoperative lactate levels on time, by groups Hyperlactatemia (HL) and not Hyperlactatemia (nHL), mean ± SD.

Of the 28 patients, 17 (60.7%) developed Hyperlactatemia (HL group). Of these, 3 patients (18%) developed eHL, and the remaining 14 developed late-onset hyperlactatemia (LHL group). The evolution of lactate values over time in the HL group as compared to those of the patients who did not develop Hyperlactatemia (nHL group) is shown in Fig. 2. The evolution of lactate values over time is shown in Figs. 3 a–d. The use of NE during the postoperative period was not associated with HL.

The comparison between baseline and intraoperative characteristics of the enrolled patients in the Early Hyperlactatemia (eHL), Late Hyperlactatemia (LHL) and Non-Hyperlactatemia groups (nHL) are shown in Table 1.

The mixed-model analysis of lactatemia over time indicated that ephedrine, phenylephrine, and intraoperative MAP were significantly associated with the development of hyperlactatemia, as shown in Table 2.

Discussion

The principal finding of this study is that use of intraoperative adrenergic agonists ephedrine and phenylephrine are associated with postoperative hyperlactatemia. The mixed model analysis confirmed that the presence of intraoperative hypotension, ephedrine dose, and use of phenylephrine were associated with postoperative hyperlactatemia.

A total of 60% of the patients evaluated developed hyperlactatemia during the first 24 postoperative hours. This finding is similar to that described in other series, although the various definitions make comparison difficult.[6–8] In that studies, most of the patients developed late hyperlactatemia, which is similar to what has been reported in the context of cardiac surgery, and has been associated to longer duration of cardio-pulmonary bypass, and use of epinephrine.[4,27,28] In our case, the variables associated with the development of hyperlactatemia were the use of ephedrine, use of phenylephrine and the presence of intraoperative hypotension.

Ephedrine is an indirect alpha 1-, beta 1-, and beta 2-agonist that is commonly used to manage intraoperative hypotension. Although this drug is used in diverse anesthesia scenarios, it is to regional obstetric anesthesia that there

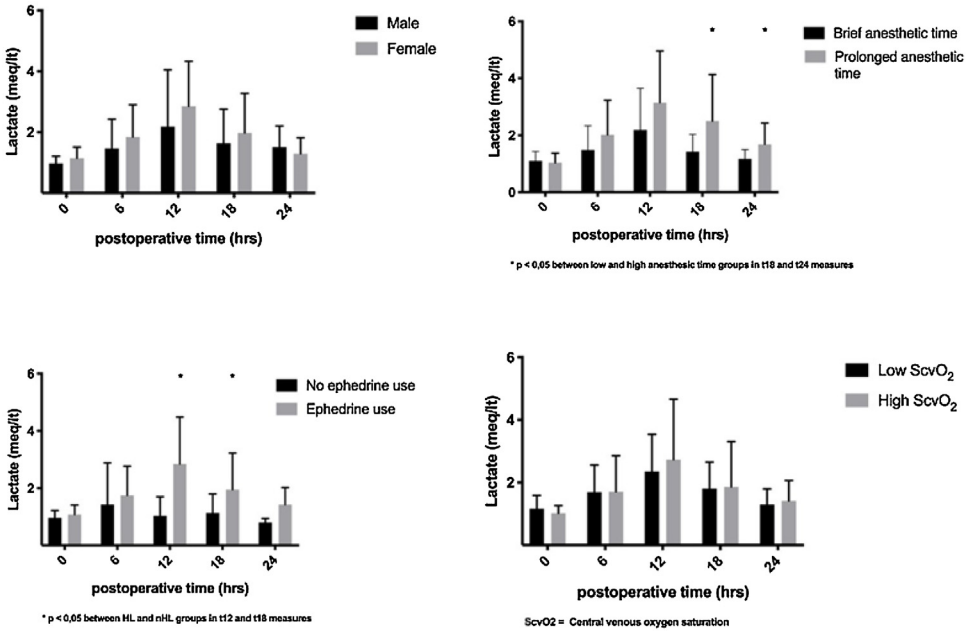

Figure 3 Postoperative lactate levels over time, by gender (a); anesthetic time (b); ephedrine group (c); and $ScvO_2$ group (d), mean ± SD.

Table 1 Comparison of baseline and intraoperative characteristics in the Early-onset Hyperlactatemia group (eHL), Late-onset Hyperlactatemia group (LHL), and non-Hyperlactatemia (nHL) groups; mean ± SD.

	nHL (n = 11)	eHL (n = 3)	LHL (n = 14)
Lactate baseline	1.0 ± 0.3		
Lactate peack ($mEq.L^{-1}$)	1.2 ± 0.4	3.0 ± 0.4[a]	3.9 ± 1.4[b]
Female gender (%)	36	67	79
Age (y.o.)	73 ± 6	76 ± 5	73 ± 9
Hypertension (%)	45	33	71
Diabetes (%)	27	33	36
Surgical time	125 ± 40	180 ± 73	177 ± 67[b]
Anesthetic time	182 ± 39	222 ± 78	241 ± 68[b]
Intraoperative fluids (mL)	1845 ± 1154	2416 ± 1233	854 ± 831
Total ephedrine doses (mg)	18 ± 16	32 ± 33	54 ± 23[b]
Total phenilephrine doses (mg)	171 ± 299	500 ± 866	721 ± 1560
Norephinephrine use	18	33	29
MAP iop (mmHg)	79 ± 8	75 ± 2	76 ± 6
$ScvO_2$ intraoperatoria	86 ± 5	76 ± 10[a]	78 ± 7[b]

nHL, non-Hyperlactatemia patients; eHL, early-onser Hyperlactatemia patients; LHL, Late-onset Hyperlactatemia patients; MAP iop, intra-operative Mean Arterial Pressure; $ScvO_2$, Central Venous Oxygen Saturation.
[a] $p < 0.05$ between nHL and Ehl.
[b] $p < 0.05$ between nHL and eHL.

Table 2 Multilevel mixed-effects linear regression analyses, with univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
	Coef	95% CI	*p*-value	Coef	95% CI	*p*-value
Gender	0.270	−0.301–0.841	0.354			
Anesthetic time	0.005	0.001–0.009	0.014	0.099	−0.220–0.418	0.543
Ephedrine	0.014	0.004–0.024	0.004	0.012	0.003–0.019	0.004[a]
MAP iop	−0.031	−0.071–0.009	0.136	−0.028	−0.052– -0.034	0.026[a]
Phenilephrine	0.000	0.000–0.000	0.001	0.000	0.000–0.000	0.001[a]
Norepinephrine	0.331	−0.310–0.973	0.311			
$ScvO_2$	−0.016	−0.053–0.021	0.401			

MAP iop, intra-operative Mean Arterial Pressure; $ScvO_2$, Central Venous Oxygen Saturation.
[a] $p < 0.05$.

are more studies of its effects on pH and lactate levels. An association between ephedrine and fetal acidosis has been reported, which is possibly attributable to placental lactate production mediated by the beta-2 receptor.[34–36]

Given its observational design, our study did not provide results that would conclusively explain the mechanisms underlying this ''ephedrine-related'' hyperlactatemia. However, the predominance of late- over early-onset hyperlactatemia and the known beta-agonist effects of ephedrine are compatible with a hyperlactatemia of ''adrenergic'' origin, which would also be consistent with the findings of the studies mentioned above.[20,23] Among commonly used adrenergic agents, only adrenaline has been linked to late-onset hyperlactatemia.[26,37] This agent is more potent than ephedrine and is generally reserved for anaphylaxis treatment, advanced cardiopulmonary resuscitation, and management of severe shock. Our study provides the first report linking other adrenergic agents, in particular ephedrine, to the development of perioperative hyperlactatemia in the context of abdominal surgery.

Phenylephrine is a direct alpha-agonist that is 82-fold more potent than ephedrine, according to studies on hypotension during spinal anesthesia for cesarean section.[38] At typical clinical dosages, this drug produces arterial vasoconstriction, which increases arterial blood pressure; due to reflex mechanisms mediated by baroreceptors, cardiac output is thereby reduced.[39] Recent reports have demonstrated potential risks of intraoperative phenylephrine, and some authors have suggested substituting this drug for norepinephrine.[40,41] The association between intraoperative hypotension and postoperative hyperlactatemia is compatible with hyperlactatemia of hypoxic origin, which is well-documented in diverse critical care populations.[42]

Finally, in agreement with findings in other contexts, our study did not document an association between norepinephrine and hyperlactatemia.[43]

Several limitations of this study should be noted. First, the sample size was modest, in a small, homogenous group of patients, using a more physiological design. Second, the findings presented here are secondary outcomes from a study designed *a priori* to identify triggers of postoperative delirium. However, this limitation is mitigated by the fact that the patient cohort was subjected to a standardized protocol for interventions and measurements, and this secondary objective was defined *a priori*. A third limitation is associated with the lack of universal consensus on anesthesia and hemodynamic management protocols. To create a standardized study protocol, the team relied on a series of widely-recommended measurements (such as the use of dynamic parameters to evaluate the need for fluids) and other local protocols (such as the use of sequential vasoactive agents and the use of the BIS system to guide anesthesia depth).

Other limitations of our study are the lack of glycemia data for the study patients, as many studies on hyperlactatemia have reported an association between hyperglycemia and hyperlactatemia. It was not possible to evaluate this relationship with the available data;[28] and by the fact that all studied patients received dexamethasone to prevent postoperative nausea and vomiting. This pharmaceutical agent has been associated with hyperlactatemia, although at a much higher dose (60 mg) than the dose used in our study patients (4 mg).[44] Finally, our findings could be influenced by confounders of postoperative care (hypotension, hemodynamic or fluid management), or other variables not measured in this period. During postoperative time, we only documented that the use of NE was not associated with the presence of PO-HL.

The strengths of the study include the use of a standard hemodynamic and respiratory management protocol. Such uniformity is uncommon in this type of study, as hemodynamic management decisions are often left to the judgment of the attending anesthesiologist on a case-by-case basis. Another strength was the use of a strong statistical approach that allowed for a comprehensive evaluation of postoperative hyperlactatemia. The analysis was able to consider a series of covariates potentially involved in the onset of this condition.

In conclusion, postoperative hyperlactatemia is a complex event determined by numerous variables, including the presence of intraoperative hypotension and the administration of agents to manage it, such as ephedrine or phenylephrine. Our study results suggest that both ephedrine and phenylephrine are associated with hyperlactatemia. This finding should be confirmed in future studies. In the meantime, as suggested by other authors, the attending team should take note of elevated postoperative lactate values and carefully evaluate the use of intraoperative adrenergic agents. Physicians should consider the timing of events and the status of other perfusion markers, including regional and global indicators, to make the optimal decision regarding resuscitation strategies for a given patient. Further studies will be necessary to elucidate the mechanisms underlying this condition, using protocols designed to address this question directly.

Conclusions

The use of the intraoperative adrenergic agents' ephedrine and phenylephrine are associated with the development of postoperative hyperlactatemia. In the multivariate model, the presence of intraoperative hypotension was also significantly associated with PO-HL. The potential impact of the use of intraoperative adrenergic agents should be considered in the interpretation of postoperative hyperlactatemia.

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Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Almeida DL, Amendola CP, Horta VM, et al. Hyperlactatemia at ICU admission is a morbid-mortality determinant in high risk noncardiac surgeries. Rev Bras Ter Intensiva. 2006;18:360–5.
2. Silva JM Jr, Ribas AM, Mendes FA, et al. Metabolic Acidosis assessment in high-risk surgeries: prognostic importance. Anesth Analg. 2016;123:1163–71.

3. Andersen LW, Holmberg MJ, Doherty M, et al. Postoperative Lactate Levels and Hospital Length of Stay After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2015;29:1454–60.
4. Ranucci M, De Toffol B, Isgrò G, et al. Hyperlactatemia during cardiopulmonary bypass: determinants and impact on postoperative outcome. Crit Care. 2006;10:R167.
5. Hu BY, Laine GA, Wang S, et al. Combined central venous oxygen saturation and lactate as markers of occult hypoperfusion and outcome following cardiac surgery. J Cardiothorac Vasc Anesth. 2012;26:52–7.
6. Kogan A, Preisman S, Bar A, et al. The impact of hyperlactatemia on postoperative outcome after adult cardiac surgery. J Anesth. 2012;26:174–8.
7. Vibert E, Boleslawski E, Cosse C, et al. Arterial Lactate Concentration at the End of an Elective Hepatectomy Is an Early Predictor of the Postoperative Course and a Potential Surrogate of Intraoperative Events. Ann Surg. 2015;262:787–92.
8. Li S, Peng K, Liu F, et al. Changes in blood lactate levels after major elective abdominal surgery and the association with outcomes: a prospective observational study. J Surg Res. 2013;184:1059–69.
9. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. Am J Physiol. 1965;209:604–10.
10. Bakker J, Coffernils M, Leon M, et al. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest. 1991;99:956–62.
11. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA. 1993;270:1724–30.
12. Bakker J, Gris P, Coffernils M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg. 1996;171:221–6.
13. Bakker J, Schieveld SJ, Brinkert W. [Serum lactate level as a indicator of tissue hypoxia in severely ill patients]. Ned Tijdschr Geneeskd. 2000;144:737–41.
14. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. Crit Care Med. 2009;37:2827–39.
15. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;182:752–61.
16. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303:739–46.
17. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock. Intensive Care Med. 2016;2017(43):304–77.
18. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol. 2004;558:5–30.
19. Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol. 2014;2:339–47.
20. Andersen LW, Mackenhauer J, Roberts JC, et al. Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc. 2013;88:1127–40.
21. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care. 2013;3:12.
22. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. Crit Care. 2014;18:503.
23. Luchette FA, Friend LA, Brown CC, et al. Increased skeletal muscle Na+, K+-ATPase activity as a cause of increased lactate production after hemorrhagic shock. J Trauma. 1998;44:796–801.
24. Levy B, Gibot S, Franck P, et al. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet. 2005;365:871–5.
25. Levy B, Desebbe O, Montemont C, et al. Increased aerobic glycolysis through beta2 stimulation is a common mechanism involved in lactate formation during shock states. Shock. 2008;30:417–21.
26. Totaro RJ, Raper RF. Epinephrine-induced lactic acidosis following cardiopulmonary bypass. Crit Care Med. 1997;25:1693–9.
27. Raper RF, Cameron G, Walker D, et al. Type B lactic acidosis following cardiopulmonary bypass. Crit Care Med. 1997;25:46–51.
28. Maillet JM, Le Besnerais P, Cantoni M, et al. Frequency, risk factors, and outcome of hyperlactatemia after cardiac surgery. Chest. 2003;123:1361–6.
29. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology. 2015;123:307–19.
30. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119:507–15.
31. Sessler DI, Sigl JC, Kelley SD, et al. Hospital stay and mortality are increased in patients having a ''triple low'' of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology. 2012;116:1195–203.
32. Tobar E, Abedrapo MA, Godoy JA, et al. Impact of hypotension and global hypoperfusion in postoperative delirium: a pilot study in older adults undergoing open colon surgery. Rev Bras Anestesiol. 2018;68:135–41.
33. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2ª ed; 2005.
34. Cooper DW, Carpenter M, Mowbray P, et al. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology. 2002;97:1582–90.
35. Cooper D, Sharma S, Orakkan P, et al. Does placental lactate production have a role in ephedrine-induced fetal metabolic acidosis? Br J Anaesth. 2008;100:727–8.
36. Ngan Kee WD, Khaw KS, Tan PE, et al. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology. 2009;111:506–12.
37. Di Giantomasso D, Bellomo R, May CN. The haemodynamic and metabolic effects of epinephrine in experimental hyperdynamic septic shock. Intensive Care Med. 2005;31:454–62.
38. Saravanan S, Kocarev M, Wilson RC, et al. Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. Br J Anaesth. 2006;96:95–9.
39. Thiele RH, Nemergut EC, Lynch C. The clinical implications of isolated alpha(1) adrenergic stimulation. Anesth Analg. 2011;113:297–304.
40. Mets B. Should Norepinephrine, Rather than Phenylephrine, Be Considered the Primary Vasopressor in Anesthetic Practice? Anesth Analg. 2016;122:1707–14.
41. Futier E, Lefrant JY, Guinot PG, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. JAMA. 2017;318:1346–57.
42. Howell MD, Donnino M, Clardy P, et al. Occult hypoperfusion and mortality in patients with suspected infection. Int Care Med. 2007;33:1892–9.
43. Levy B, Perez P, Perny J, et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med. 2011;39:450–5.
44. Ottens TH, Nijsten MW, Hofland J, et al. Effect of high-dose dexamethasone on perioperative lactate levels and glucose control: a randomized controlled trial. Crit Care. 2015;19:41.