The effect of hyperlactatemia timing on the outcomes after cardiac surgery

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Abstract

Background: Several studies linked postoperative hyperlactatemia to worse outcomes in adult patients undergoing cardiac surgery. However, data on the effect of timing of hyperlactatemia on outcomes are scarce. We sought to determine the prevalence of early hyperlactatemia (EHL) and its impact on clinical outcomes compared to late hyperlactatemia (LHL) in patients undergoing ACS procedures.

Results: We included 305 consecutive adult patients who underwent cardiac surgery procedures between July 2017 and Nov 2019 at a single institution. Lactate level was measured in the first 10 h after surgery and EHL was defined as lactate level > 3 mmol/L in the first hour after surgery. Logistic regression analysis was performed to determine predictors of EHL. Seventeen percent (n = 52) had EHL while 83% (n = 253) did not. Patients with EHL had significantly longer cardiopulmonary bypass (P = 0.001) and cross-clamp (P = 0.001) times due to increased surgical complexity in this group. Early hyperlactatemia was associated with increased post-operative extracorporeal membrane oxygenation (ECMO) support (0% vs 5.7%, P < 0.001), longer intensive care unit stay (P = 0.004), and increased hospital mortality (0% vs. 3.8%, P = 0.009). Cardiopulmonary bypass time (OR 1.001; 95% CI 1.011–1.012, P = 0.02) and glucose level (OR 1.2; 95% CI 1.1–1.3, P = 0.003) were independently associated with increased rate of EHL. In contrast, diabetes mellitus (OR 0.26; 95% CI 0.12–0.55, P < 0.001) significantly attenuated the rate of EHL.

Conclusions: Early hyperlactatemia after cardiac surgery was associated with increased morbidity and mortality. Late hyperlactatemia was very common and had a self-limiting and benign course.

Keywords: Lactate, Cardiac surgery, Early hyperlactatemia, Late hyperlactatemia

Background

Lactate level is a robust biomarker and strong predictor of clinical outcomes in patients undergoing open-heart surgery and in critically ill patients [1–5]. Several studies confirmed the prognostic value of hyperlactatemia (HL) after cardiac surgery in predicting mortality and major morbidity [3, 6–12].

However, new evidence suggests that not all forms of HL are harmful after cardiac surgery [13, 14]. Maillet and colleagues found that the timing of HL plays a major role where patients with an immediate postoperative increased lactate level had worse outcomes compared to patients who developed hyperlactatemia late after surgery [13]. Therefore, the timing of hyperlactatemia (early versus late) may have different underlying mechanisms and different impacts on clinical outcomes after cardiac surgery. Indeed, conventional understanding suggests that stress-induced HL is due to anaerobic glycolysis as a result of tissue hypoperfusion, hypoxia, or both. However, recent studies linked some forms of stress HL to increased aerobic lactate production secondary to increased adrenergic stimulation, with or without decreased lactate clearance [1]. Thus, it seems that not all patterns of hyperlactatemia are harmful after cardiac surgery and that the timing of hyperlactatemia is one potential confounder of benign versus detrimental hyperlactatemia.
The purpose of the present study is to bridge this gap in knowledge by shedding light on the prevalence, predictors, and clinical consequences of early compared to late hyperlactatemia in adult patients undergoing cardiac surgery.

Methods

Patient population, study design, and outcomes

This is a retrospective observational study. Clinical, operative, and outcome data were collected prospectively in a computerized database, and all consecutive adult patients (July 2017 to November 2019) undergoing open cardiac surgery procedures by one surgeon (KDA) were selected from the database and included in this study (N = 305). Data that were not included in the prospective database were collected retrospectively from electronic charts which include data about lactate levels (mmol/L) during the first 12 h after arrival to the intensive care unit (ICU) as well as the glucose (mmol/L) and arterial PH level upon arrival to the ICU. Procedures included isolated coronary artery bypass grafting (CABG); isolated single, double, and triple valve surgery; combined CABG and valve(s) procedures; and other procedures such as aortic dissection, aortic root replacement, and surgery for mechanical complications of myocardial infarction. Both first time and redo procedures (including multiple redo procedures) were included.

The study was approved by our institutional Research Ethics Board and the individual’s consent for the study was waived. Early hyperlactatemia (EHL) was defined as a lactate level > 3 mmol/L during the first hour upon arrival to the intensive care unit. Late hyperlactatemia (LHL) was defined as lactate level > 3 mmol/L that develops after 1 h of arrival to the intensive care unit. The lactate cut-off value of 3 mmol/L for defining HL was based on previous literature that suggested a range of 3–5 mmol/L to define significant hyperlactatemia after cardiac surgery [14]. In addition, we determined this cut-off value based on receiver operating characteristic (ROC) curve analysis for postoperative lactate level in our study during the first hour after surgery and its association with postoperative mortality and major adverse cardiac and cerebrovascular events.

The primary outcome was hospital mortality which was defined as any postoperative death in hospital.

Anesthetics, cardiopulmonary bypass, and operative management

Details of anesthesia, cardiopulmonary bypass, cardioplegia, and operative management are provided in the Supplement (Sections 1 and 2).

Lactate level measurement (mmol/L)

To evaluate trends of lactate level, data on lactate levels were retrospectively collected for all patients for the first 12 h after arrival to the ICU. Lactate data beyond 10 h had large percentage of missing data (> 30%) as it was not consistently measured beyond 10 h. Therefore, lactate data for hours 11 and 12 were excluded. Missing values for other lactate data during the first 10 h after surgery were low (2.9%). Missing data analysis was performed using multiple imputations as detailed below.

Statistical analysis

Statistical analyses were performed with SPSS version 25 (SPSS, IBM, Armonk, NY, USA). The two groups were compared for statistical significance based on chi-square or Fisher’s exact test for categorical variables which are expressed as percentages. All continuous variables were explored for normality using normality diagnostics (histograms, skewness, and kurtosis). Student’s t test was used to analyze continuous variables that were normally distributed, and the Mann-Whitney U test was used for variables that had non-normal distributions. Continuous variables were expressed as means (SD) or median with (25th and 75th percentile) as appropriate. Statistical significance was based on a two-tailed P value of less than 0.05.

Univariable and multivariable logistic regression model was employed to evaluate the independent predictors of EHL (dependent variable). A repeated measures analysis was used to test the main effect of postoperative time (hours), HL group, and the time × group interaction to determine the change in lactate levels over the 10 time points by HL group (early versus late). In addition, the repeated measures analysis was used to determine the predictors of postoperative lactate levels where the response (dependent) variables are the lactate levels during the first 10 h after surgery and the between-subjects factor is diabetes mellitus while adjusting for glucose level and cardiopulmonary bypass time as covariates.

Details of univariable and multivariable logistic regression as well as repeated measures analysis are described in the Supplement (Sections 3 and 4).

Missing data analysis

A multiple imputation (5 imputations) to impute the 6.3% missing data points for all variables using Markov chain Monte Carlo multiple imputation method was employed. Details are provided in the Supplement (Section 5).

Results

Demographics and baseline clinical profile

Seventeen percent (n = 52) of the patients developed postoperative EHL while 83% (n = 253) did not. Of
patients with no EHL, 70.8% (n = 179) had LHL. Only 24.3% (n = 74) of the entire population of this study did not develop postoperative hyperlactatemia (a lactate value < 3 mmol/L). Thus, even though EHL was not frequent after cardiac surgery, LHL was very common. The prevalence of diabetes mellitus was significantly lower in the EHL group compared to the LHL group (30% vs 51.4%, P = 0.006). There was a higher surgical complexity in the EHL group where the prevalence of combined CABG and valve(s) procedures was higher in the EHL group (21% vs. 9.5%, P = 0.038). There were no other significant differences between the two groups in other baseline characteristics. Details of patients’ baseline characteristics are presented in Table 1.

Table 1 Demographics and baseline clinical profile

| Variable                  | Early hyperlactemia | P value |
|---------------------------|----------------------|---------|
| No. of patients           | (253) (52)           |         |
| Age (years)               | 54.3 ± 0.28          | 0.79    |
| BSA                       | 1.84 ± 0.29          | 0.45    |
| BMI                       | 29.3 ± 6.6           | 0.32    |
| Female                    | 37.5% (95)           | 0.52    |
| Euro Score ES II          | 3.5 ± (4.5)          | 0.94    |
| Diabetes mellitus         | 51.4% (129)          | 0.006   |
| Metformin use             | 24.5% (62)           | 0.15    |
| Hypertension              | 53.6% (134)          | 0.96    |
| Creatinine clearance      | 97.1 ± 38.5          | 0.52    |
| ESRD on dialysis          | 2.4% (6)             | 0.50    |
| Operation category        |                      | 0.038   |
| Isolated CABG             | 35.2% (89)           |         |
| Isolated valve(s)         | 49.2% (124)          |         |
| Combined CABG + valve(s)  | 9.5% (24)            |         |
| Othersb                   | 6% (15)              |         |
| Cardioplegia type         |                      | 0.96    |
| Del Nido                  | 75.8% (191)          |         |
| Cold blood                | 24.2% (61)           |         |
| Atrial Fibrillation       | 19.1% (48)           | 0.64    |
| Ejection Fraction         | 50.1 ± (9.4)         | 0.64    |
| Redo surgery (first and multiple) | 11.1% (28)       | 0.47    |
| Preoperative TIA or stroke| 4% (10)              | 0.50    |
| Systolic PAP (mmHg)       | 38.5 ± 17            | 0.57    |
| Hemoglobin (mg/dL)        | 12.3 ± 2.2           | 0.40    |

BSA body surface area, BMI body mass index, MI myocardial infarction, LVEF left ventricular ejection fraction
*This includes single, double, or triple valve repair and/or replacements
**Others include aortic root replacement, ascending aorta, or aortic arch interventions such as type A dissection repair, post-myocardial VSD closure, and LV aneurysm repair, among others

Table 2 Operative profile and postoperative outcomes

| Variable                  | Early hyperlactemia | P value |
|---------------------------|----------------------|---------|
| Intraoperative variables  |                      |         |
| Duration of CPB (min)     | 150 ± 56             | 0.001   |
| Clamp time (min)          | 120 ± 44             | 0.001   |
| Postoperative outcomes    |                      |         |
| Operative mortalitya      | 0 (0)                | 3.7% (2) | 0.009 |
| ECMO                      | 0 (0)                | 5.7% (3) | < 0.001 |
| IABP                      | 3.2% (8)             | 7.7% (4) | 0.10  |
| Metabolic acidosis        | 2.8% (7)             | 17.3% (9)| < 0.001 |
| Peak troponin T level (ng/mL) | 0.9 (0.65–1.4)    | 1.1 (0.7–1.8) | 0.03 |
| Stroke                    | 0.8% (2)             | 5.7% (3) | 0.048 |
| AKI requiring dialysis    | 2% (5)               | 1.9% (1)| 0.98 |
| Deep sternal infection    | 0(0)                 | 5.7% (3) | < 0.001 |
| ICU length of stay (days) | 3 (2–5)              | 5 (3–6.5) | 0.004 |
| Hospital length of stay   | 9 (7–14)             | 10 (7–17) | 0.02 |

Metabolic acidosis was defined as a pH ≤ 7.3 with low HCO3 (< 22 mEq/L) on ABG during the first 10 h after surgery. Postoperative AKI was defined as any new postoperative renal failure that requires dialysis. AKI acute kidney injury, CPB cardiopulmonary bypass, ECMO extracorporeal membrane oxygenation, ICU intensive care unit.

Patterns of postoperative hyperlactatemia

Two distinguished patterns of HL were identified. Early hyperlactatemia (EHL) started early and these patients arrived to the intensive care unit with high lactate level, reached peak level at 3 h, and then started to decrease 5 h after ICU admission. In contrast, LHL developed few

Operative profile and postoperative outcomes

Cardiopulmonary bypass (181 (54) vs. 150 (56), P = 0.001) and aortic cross clamp (144 (49) vs. 120 (44), P = 0.001) times were significantly higher in the EHL group which is explained by the more prevalence of complex procedures in the EH group.

Early hyperlactatemia was associated with significant increase in mortality (3.7% vs. 0%, P = 0.009) and marked increase in the requirement for postoperative extracorporeal membrane oxygenation (ECMO) support (P < 0.001). Likewise, there was a sixfold increase in the rate of metabolic acidosis in the EHL group. Similarly, the prevalence of other postoperative complications such as stroke and surgical site infections was significantly higher in the EHL group. As a result, postoperative intensive care unit stay and hospital length of stay were both significantly longer in the EHL group. Operative and postoperative profiles are detailed in Table 2. Of note, there was almost 2.5-folds increase in the rate of postoperative IABP in the EHL group (7.7% vs. 3.2%). However, this difference did not reach a statistical significance (P = 0.1) with our current sample size.
hours after arrival to the ICU, peaked at 7 h after ICU admission, and then started to decline after that. Details of patterns of HL are depicted in Fig. 1. Estimated marginal means for lactate levels with the 95% CI for each time point in both groups are detailed in the Supplement (Table S1).

Effect of blood glucose level on postoperative lactate levels
There was a positive relationship between glucose levels and lactate levels which is influenced by diabetes mellitus. Diabetes mellitus attenuated this relationship where a 1 mmol/L increase in glucose level was associated with 14 and 26% increase in the lactate level in patients with and without diabetes, respectively. This relationship is depicted in a scatter plot in Fig. 2.

Effect of diabetes mellitus on postoperative lactate levels
Importantly, diabetes mellitus was associated with a significant attenuation of lactate levels after cardiac surgery. As shown in Fig. 3, postoperative lactate levels were significantly lower in patients with diabetes mellitus ($P < 0.001$). Estimated marginal means for lactate levels with the 95% CI for each group in both groups are detailed in the Supplement (Table S2). This negative association between DM and lactate levels is evident despite the fact that DM is associated with higher rate of hyperglycemia and higher glucose levels (mean glucose level is 10.1 (2.7) and 7.9 (2.6) mmol/L, $P < 0.001$) in patients with and without diabetes, respectively. The explanation for this important finding is detailed in the “Discussion” section.

Predictors of early hyperlactatemia
A logistic regression model was used to evaluate independent predictors of EHL. First, a univariable logistic regression model was employed to screen potential variables. All variables that had a $P$ value of $< 0.2$ were included in a multivariable logistic regression model using the backward elimination method. On univariable analysis, glucose level, CPB time, cross-clamp time, and surgical complexity were all predictors of increased rate of EHL. In contrast, DM was a significant and strong predictor of lower rate of EHL (OR = 0.39; 95% CI, 0.20–0.75; $P = 0.005$).

On multivariable analysis, independent predictors of EH included glucose level (OR = 1.3; 95% CI, 1.1–1.3; $P = 0.003$), CPB time (OR = 1.02; 95% CI, 1.01–1.1; $P = 0.015$), and DM (OR = 0.26; 95% CI, 0.12–0.55; $P < 0.001$). Univariable and multivariable predictors are shown in Table 3, and the details of multivariable analysis methods including selection method, model calibration, model discrimination, and collinearity evaluation are described in Table 3 footnote and the Supplement (Section 3).

Discussion
In the present study, we examined the timing patterns of postoperative hyperlactatemia and their consequences in adult patients undergoing cardiac surgery. We found that early but not late hyperlactatemia was associated

![Fig. 1 Patterns of hyperlactatemia after cardiac surgery. Bars represent the 95% confidence intervals. The lactate levels change over time and it is significantly different in both groups (within-subjects $P$ value $< 0.001$). Similarly, lactate levels are significantly different between the two groups at all time points (between-subjects $P$ value $< 0.001$). Estimated marginal means for lactate levels with the 95% CI for each time point in both groups are detailed in the Supplement (Table S1).](image-url)
Fig. 2 Scatter plot for the relationship between glucose levels in mmol/L and the lactate levels in mmol/L stratified by diabetes mellitus. There is a positive relationship between the glucose level and the lactate level which is attenuated in patients with diabetes mellitus where a 1-mmol/L increase in glucose level is associated with 14 and 26% increase in the lactate level in patients with and without diabetes, respectively. The solid lines represent the fit lines for each category based on diabetes mellitus and the dotted lines represent the 95% confidence intervals.

Fig. 3 The effect of diabetes mellitus on postoperative lactate levels while controlling for the effect of covariates (CPB time and glucose level). DM is associated with a significant attenuation of the postoperative lactate levels ($P < 0.001$). CPB indicates cardiopulmonary bypass. 95% CI indicates 95% confidence interval. DM indicates diabetes mellitus. Estimated marginal means for lactate levels with the 95% CI for each time point in both groups are detailed in the Supplement (Table S2).
with increased mortality and morbidity. We also found that complexity of the procedure and cardiopulmonary bypass time and glucose level are important predictors of increased risk of EHL while diabetes mellitus attenuates this risk. Importantly, late hyperlactatemia (LHL) was very common after cardiac surgery and was benign and self-limiting.

Several studies have examined and confirmed the prognostic value of postoperative lactate levels in predicting mortality and morbidity after cardiac surgery [1,2,7,15,16]. However, these studies did not differentiate between different timing patterns of HL. The incremental finding from the present study is that the timing of hyperlactatemia is a critical determinant of its consequences where EHL is usually detrimental and needs aggressive treatment while LHL is usually benign and tends to resolve spontaneously. Our findings are in agreement with a study by Maillet and colleagues who found that immediate hyperlactatemia occurring on ICU admission was associated with fourfold increased risk of mortality ($P < 0.001$) compared to late hyperlactatemia [13].

The association of EHL but not LHL with increased morbidity and mortality in the present study may indicate different etiologies of HL in the two patterns. Anaerobic metabolism secondary to tissue hypoperfusion is the prevailing mechanism in the literature and perhaps represents the main etiology in EHL [7,9,17]. Indeed, the rate of metabolic acidosis was markedly higher in the patient with EHL in our study. Nonetheless, the etiology of hyperlactatemia after cardiac surgery is likely to be multifactorial. Large proportion of patients in the present study had no EHL but developed LHL several hours after arrival to the intensive care unit which did not increase the risk of morbidity or mortality. Increased lactate levels may occur under aerobic conditions secondary to increased catecholamine and inflammatory mediators after cardiac surgery without significant tissue hypoperfusion, and this latter mechanism may be the principle etiology of LHL [1].

The association of EHL with increased mortality and morbidity is perhaps linked to some extent to the acidifying effect of lactate. Indeed, metabolic acidosis was sixfolds higher in the patient with EHL compared to patients with LHL in our study. Metabolic acidosis leads to cellular dysfunction, myocardial depression, and hemodynamic compromise [16]. This may explain the significantly higher rate of postoperative ECMO support and mortality in patients with EHL in our study.

Cardiopulmonary bypass and aortic cross-clamp times were important predictors of EHL. Both are usually indicative of more complex or complicated cardiac procedures. Indeed, on univariable analysis, more complex procedures such as combined coronary and multiple valve procedures were strongly associated with increased risk of EHL. The longer the duration of CPB and clamp times, the higher the likelihood of sustaining systemic end-organ hypoperfusion which induces a state of anaerobic metabolism with increased glycolysis and lactate production. In addition, longer CPB time provokes systemic inflammatory response and induces cytokine and stress hormone release which leads to hyperglycemia and increased lactate production [18].

Glucose level was also an important predictor of lactate levels. Both lactate and glucose are involved in carbohydrate metabolism, and they serve as precursors for biosynthesis of one another [17]. Similarly,
hyperlactatemia and hyperglycemia are common metabolic manifestations of response to stress induced by cardiac surgery and other major procedures [1, 2, 15]. Each 1-mmol increase in the glucose level was associated with 11% increase in the lactate level. Interestingly, diabetes mellitus strongly attenuated this relationship between glucose and lactate where each 1-mmol increase in the glucose level was associated with 14% increase in the lactate level in diabetic patients compared to 26% increase in the lactate level in non-diabetics. This may seem counter-intuitive as patients with diabetes are more likely to have hyperglycemia and therefore DM should presumably have a positive effect on lactate level. Nonetheless, DM had actually a suppressing effect on lactate level. Indeed, postoperative lactate levels (Fig. 3) are significantly attenuated by diabetes mellitus. Similar to our findings, Greco and associates evaluated the relationship between hyperlactatemia, glucose, and diabetes in 4098 patients after cardiac surgery and found that stress-induced increase in lactate levels is strongly attenuated in patients with DM [7]. Moreover, this suppressing effect of DM on stress hyperlactatemia has been also reported with stress hyperglycemia in several studies where the association between hyperglycemia and adverse outcomes is strongly suppressed in patients with DM [19–21].

These findings suggest that DM may grant a degree of protection against HL in patients undergoing cardiac surgery which is independent of the glucose level, surgical complexity, and CPB duration, among other confounders. Although mechanisms for this suppressing effect of DM on stress-induced hyperlactatemia are not fully understood, it can be to some extent explained by the state of relative insulin deficiency in patients with DM which leads to inhibition of glycolysis and lactate production since insulin is a positive regulator of glycolysis [7, 22]. Likewise, gluconeogenesis is inhibited by insulin, and therefore, with relative insulin deficiency in diabetic patients, gluconeogenesis pathway is stimulated and lactate utilization is increased through the lactic acid cycle resulting in increased lactate clearance [23]. Thus, the net result of relative insulin deficiency in diabetic patients is a reduction in synthesis and increase in utilization of plasma lactate by glycolysis inhibition and gluconeogenesis acceleration, respectively.

Our study has important clinical implications. First, the timing of HL, in our view, is the most important determinant of prognostic value of lactate levels after cardiac surgery. Early HL was strongly predictive of complications in the present study which may reflect end-organ hypoperfusion and tissue hypoxia as primary etiology in early HL. Therefore, EHL should be managed aggressively in order to reverse end-organ hypoperfusion and tissue hypoxia. In contrast, LHL occurred very commonly and was not associated with increased mortality or morbidity. Second, patients with DM may not exhibit significant HL despite significant tissue hypoperfusion as DM appears to mask and attenuates stress-induced hyperlactatemia. Thus, when the lactate level is used in evaluating end-organ perfusion in diabetic patients, this suppressing effect of DM on the lactate level should be considered.

Limitations
Our study has several limitations. This is an observational single-center retrospective study which makes it susceptible to inherent selection and information biases. However, the prospective nature of the data collection adds strength to the internal validity of the study. We attempted to use rigorous statistical regression analysis to control for confounders; however, we admit that regression analysis accounts only for known confounders that are included in the multivariable model and does not account for unknown or unmeasured confounders. Finally, we reported only short-term outcomes and whether EHL is associated with any long-term consequences is unknown from the present study.

Conclusions
After cardiac surgery, early but not late hyperlactatemia could be associated with increased morbidity and mortality. Increased surgical complexity, hyperglycemia, and cardiopulmonary bypass time were positive independent predictors of EHL. Diabetes mellitus significantly attenuated stress-induced hyperlactatemia after cardiac surgery, and this masking effect of DM on lactate level should be considered when lactate is used as a biomarker in evaluating end-organ perfusion in diabetic patients.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s43057-020-00029-w.

Additional file 1: Supplement. Table S1. Estimated marginal means with 95% CI of lactate levels during the first 10 hours after cardiac surgery in patients with early and late patterns of hyperlactatemia. Table S2. Estimated marginal means with 95% CI of lactate levels during the first 10 hours after cardiac surgery in patients with and without diabetes mellitus. Adjusted for CPB time and Glucose level.

Abbreviations
CABG: Coronary artery bypass grafting; EHL: Early hyperlactatemia; HL: Hyperlactatemia; LHL: Late hyperlactatemia

Acknowledgements
Juan J Alfonso collected, maintained, and managed the adult cardiac surgery database from which the data for this study is generated.

Author's contributions
KDA designed the study, analyzed the data, and wrote and approved the final manuscript.
Funding
None

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The research ethics board approved the study (R20013) and individual consent was waived.

Consent for publication
Not applicable

Competing interests
None

Received: 9 July 2020 Accepted: 11 August 2020
Published online: 20 August 2020

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