Cardiology in the Young

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Poor correlation of venous lactate with systemic oxygen saturation in the paediatric cardiac ICU: a pilot study

Rohit S. Loomba[1,2], Enrique G. Villarreal[3], Angela Klein[2], Juan S. Farias[4], Saul Flores[5] and Nina Censoplano[1]

[1]Division of Cardiology, Advocate Children's Hospital, Oak Lawn, IL, USA; [2]Chicago Medical School at Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA; [3]Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo Leon, Mexico; [4]Children's Mercy Hospital, Kansas City, MO, USA and [5]Texas Children's Hospital/Baylor College of Medicine, Division of Critical Care, Houston, TX, USA

Original Article

Cite this article: Loomba RS, Villarreal EG, Klein A, Farias JS, Flores S, and Censoplano N (2024). Poor correlation of venous lactate with systemic oxygen saturation in the paediatric cardiac ICU: a pilot study. *Cardiology in the Young*, page 1 of 5. doi: 10.1017/S1047951124026805

Received: 8 November 2023
Revised: 27 May 2024
Accepted: 19 September 2024

Keywords:
cardiac output; lactic acid; paediatric ICUs; haemodynamic monitoring; paediatrics

Corresponding author:
Enrique G. Villarreal;
Email: quique_villarreal93@hotmail.com

Abstract

Introduction: Cardiac intensive care providers require a comprehensive understanding of cardiac output and oxygen delivery. The estimation of cardiac output in clinical practice often relies on thermodilution and the Fick principle. Central venous saturation and lactate levels are commonly used indicators for cardiac output assessment. However, the relationship between venous lactate levels and venous oxygen saturation in paediatric cardiac intensive care patients remains unclear. *Methods:* This is a single-centre retrospective pilot study aimed to investigate the correlation between venous lactate and venous oxygen saturation in paediatric patients. Data collected included venous saturation, heart rate, mean arterial blood pressure, arterial saturation by pulse oximetry, cerebral and renal near-infra-red spectroscopy values, and the presence of a functionally univentricular heart. Statistical analyses included Bayesian Pearson correlation and regression analyses. *Results:* A total of 203 data points from 37 unique patients were included in the analysis. There was no significant correlation between serum lactate and venous saturation (correlation coefficient = –0.01; Bayes factor 10 = 0.06). Serum lactate also did not correlate with other haemodynamic metrics. Venous saturation showed correlations with arterial saturation and cerebral and renal near-infra-red spectroscopy. Regression analysis revealed that parallel circulation, arterial saturation, and cerebral near-infra-red spectroscopy were predictive of venous saturation. The following equation resulted from the regression analysis: 68.0 – (12.7 x parallel circulation) – (0.8 x arterial saturation) + (0.3 x cerebral near-infra-red spectroscopy). This model had a Bayes factor 10 of 0.03 and adjusted *R*-squared was 0.29. *Conclusion:* In paediatric cardiac intensive care patients, there is no significant correlation between venous lactate and venous saturation, suggesting that lactate may not be a reliable marker for assessing the adequacy of oxygen delivery in this population. Only a weak correlation could be identified once the venous saturation was 70% or lower. Additional research is needed to explore alternative markers for monitoring oxygen delivery in critically ill paediatric patients.

Introduction

A clear understanding of cardiac output and oxygen delivery is essential for providers in the cardiac ICU. The most applied principles for cardiac output estimation in clinical practice are thermodilution and the Fick principle. Critical care providers heavily rely on central venous saturation and lactate for cardiac output estimation. However, the question of whether venous lactate levels are correlated with venous oxygen saturation has been the focus of significant inquiry. While previous research in adults after surgery has yielded conflicting results regarding the correlation between lactate and oxygen delivery, in paediatrics, this question remains largely unanswered.[1,2]

The primary aim of this study was to determine if there is a correlation between venous lactate and venous oxygen saturation in children in the cardiac ICU. The secondary aim was to determine if there was an independent association between venous lactate and venous oxygen saturation.

Methods

Study design

This study protocol was approved by the institutional review board. It is in concordance with the Helsinki Declaration. This study was a single-centre, retrospective pilot study aimed to characterise the correlation between the venous lactate and the venous oxygen saturation.

Variables of interest

The variables of interest collected were as follows: venous saturation, venous saturation, heart rate, mean arterial blood pressure, arterial saturation by pulse oximetry, cerebral near infra-red spectroscopy, and renal near infra-red spectroscopy. The presence or absence of a functionally univentricular heart was also collected. Functionally univentricular hearts were defined as those with parallel circulation, Glenn circulation, or Fontan circulation. Parallel circulation was defined as any circulation in which the saturation of blood going to the pulmonary and systemic circulations was equal.

Venous saturations were obtained by use of femoral lines terminating in the inferior vena cava. Line placement was confirmed by radiographs.

Two- site near infra-red spectroscopy values were collected. A cerebral and renal value was collected. Near infra-red spectroscopy values were obtained using the Casmed FORE-SIGHT ELITE® tissue oximeter (CAS Medical Systems, Inc., Branford, CT, USA). Heart rate, mean arterial blood pressure, arterial saturation by pulse oximetry, cerebral near infra-red spectroscopy, and renal near-infra-red spectroscopy were collected as an average of these values for the 20 minutes preceding when the venous blood gas was obtained. Blood glucose values were included with time points if collected within 20 min before or after the specific timepoint.

Patient selection

Patients under 18 years of age who were cared for in the paediatric cardiac ICU from September 1, 2022 to February 1, 2023. The beginning of this time period coincides with when T3 was first implemented at the institution. By virtue of the primary aim of this study, only patients with a venous line in place from which a blood gas was drawn were eligible for inclusion. Exclusion criteria included those over 18 years of age, those without a venous line in place, and those who did not have dates captured by T3.

Statistical analyses

Analyses were conducted on a time point level such that the sample size of the analyses was equal to the number of time points for which data were collected and not patient number. Some patients had data available for multiple time points.

Continuous variables were described as median and range while described variables were described as absolute count and frequency. Bayesian Pearson correlation was conducted to determine the univariable correlations between serum lactate, venous saturation, cerebral oxygen extraction ratio, renal oxygen extraction ratio, arterial saturation, heart rate, and blood pressure. A correlation coefficient of greater than 0.70 was considered to demonstrate a strong correlation, between 0.50 and 0.70 a moderate correlation, between 0.30 and 0.50 a weak correlation, and less than 0.30 a negligible correlation.

Next, a Bayesian regression was conducted with venous saturation as the dependent variable and the presence of parallel circulation, age in months, serum glucose, venous serum lactate, arterial saturation, heart rate, and mean arterial pressure as the independent variables. As no previous data were present to develop a prior with, the Jeffreys Zellner Siow prior was utilised. A posterior distribution was characterised for each independent variable and a posterior mean and 95% credible interval were calculated for each independent variable.

Finally, a piecewise regression was conducted to determine whether or not there was a "threshold effect" of venous saturation and serum lactate, wherein at a certain venous saturation and below, the lactate began to increase more so than at higher venous saturation levels. To do this, a locally weighted scatterplot smoothing curve was constructed. A range of potential breakpoints was evaluated using the method of least squares to minimise the mean squared error of the resulting regression model. For each candidate breakpoint, two separate linear regression models were fitted: one for the venous saturation less than or equal to the breakpoint and the second for a venous saturation greater than the breakpoint. The optimal breakpoint was then determined by identifying the model with the lowest mean squared error. The best-fitting model was then used to describe the relationship between the venous saturation and the venous lactate levels before and after the identified threshold.

All analyses were conducted using SPSS version 29.0. *P*-values do not appear as they are not part of the Bayesian statistical framework. Details of Bayesian statistics compared to frequentist is beyond the scope of this manuscript. But in brief, Bayesian statistics uses observed data to determine the probability of specific states of the dependent and independent variables. The Bayes factor provides an assessment of the strength of evidence for either the null hypothesis or the alternative hypothesis. A Bayes factor 10 of less than 0.1 indicates substantial evidence for accepting the null hypothesis, while a Bayes factor of greater than 10 indicates substantial evidence for accepting the alternative hypothesis. The posterior mean provides a point estimate while the 95% credible interval offers a range of values between which 95% of the data reside. Bayesian analyses can use previous data to help guide current analyses by using them as a prior. If a prior cannot be developed based on previously available data, then default priors can be used. In general, the Bayesian framework focuses more on presenting probabilities for different hypotheses rather than trying to prove or disprove a single hypothesis. Bayesian methods provide better-fitted models with more intuitive results. The benefits of Bayesian methods over frequentist methods with respect to clinical research are highlighted elsewhere and Bayesian methods have become the recommended approach for clinical trials in consensus statements developed by popular clinical societies. Technical considerations in regard to computing power have made it more difficult in the past for Bayesian methods to be used but modern computer processors can handle such analyses without difficulty. Such methods are now being incorporated into popular statistical software as well.

Results

Cohort characteristics

A total of 203 data points were included in these analyses. The median age was 6 months. Of these 203 data points, 110 (54%) were from functionally univentricular patients. Of these 203 data points, 98 (48%) were from patients with parallel circulation. The 203 data points were from 37 unique patients. It is important to note that the sample size here is 203 as each venous lactate and venous oxygen saturation data pair is its own "sample."

The median venous saturation was 65% and the median serum lactate was 1.3 mmol/L. Figure 1 is a histogram demonstrating the venous saturation data. The venous saturation was most often between 59% and 69%.

https://doi.org/10.1017/S1047951124026805 Published online by Cambridge University Press

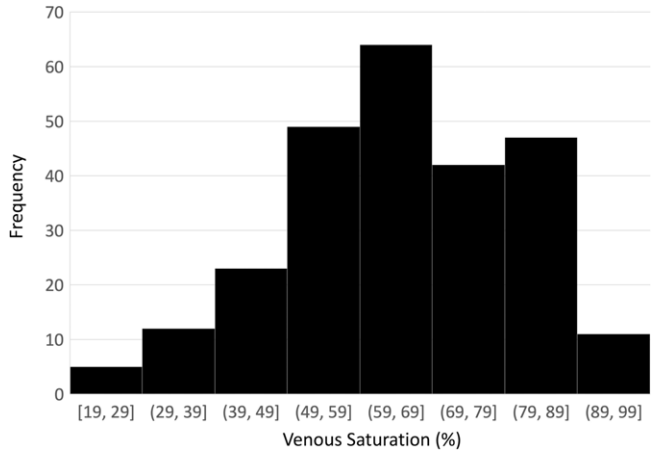

Figure 1. Histogram presenting venous saturation data.

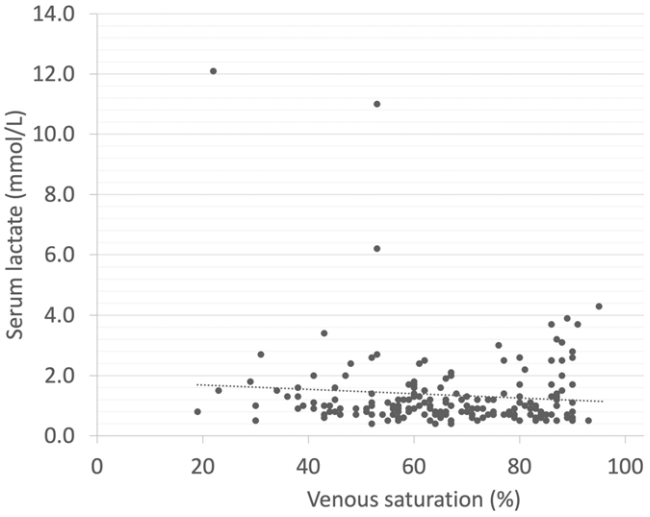

Figure 2. Scatterplot of the correlation between venous saturation and serum lactate.

Bivariate correlation analyses

With respect to serum lactate and venous saturation, there was strong evidence to support the absence of a correlation between the two (correlation coefficient = -0.01, Bayes factor 10 = 0.06). Figure 2 is a scatterplot illustrating the correlation, or lack thereof, between venous saturation and serum lactate. Serum lactate and blood glucose levels demonstrated weak correlation (correlation coefficient = 0.44, Bayes factor 10 = 10.22)

No significant correlation was found between serum lactate and heart rate, mean arterial pressure, arterial saturation, cerebral oxygen extraction ratio, or renal oxygen extraction ratio.

Venous saturation had a significant correlation with arterial saturation (moderate positive correlation), cerebral near infra-red spectroscopy (strong positive correlation), and renal near-infra-red spectroscopy (weak positive correlation). Of note, there was strong evidence to support the absence of a correlation between venous saturation and mean arterial pressure.

Regression analysis

Regression analysis with serum lactate as the dependent variable demonstrated that the most predictive model included parallel circulation, arterial saturation, and cerebral near-infra-red spectroscopy. Venous saturation, renal near-infra-red spectroscopy, mean arterial pressure, and age were not retained in the model. The following equation resulted from the regression analysis: 68.0 – (12.7 x parallel circulation) – (0.8 x arterial saturation) + (0.3 x cerebral near-infra-red spectroscopy). This model had a Bayes factor 10 of 0.03, indicating strong evidence supporting the null hypothesis. The adjusted R-squared for the model was 0.29.

Threshold analysis

The threshold analysis identified an optimal breakpoint of 70.43 for the venous saturation. A slightly greater increase in lactate values was seen below this value than above this value. The mean squared error was 3.49. The correlation coefficient for venous saturation and lactate below this threshold was -0.240, indicating a statistically significant, weak correlation between venous saturation and lactate. No significant correlation existed between the paired values when the venous saturation was greater than 70.43.

Discussion

These analyses demonstrate that serum lactate is not significantly associated with oxygen delivery metrics, including venous saturation, cerebral oxygen extraction ratio, and renal oxygen extraction ratio. Serum lactate was also found not to be significantly associated with other conventional haemodynamic metrics including heart rate, blood pressure, or arterial saturation after regression analyses were conducted.

These data demonstrate that serum lactate may not be a robust marker of systemic oxygen delivery in paediatric patients cared for in a cardiac ICU. It must be noted that a significant but weak correlation was noted between venous saturation and serum lactate when the venous saturation was below 70%. There are limited data regarding this in any patient population, particularly in paediatrics.[3–6] Klee and colleagues studied 93 paediatric patients after cardiac surgery with cardiopulmonary bypass, with each patient getting a gas immediately upon ICU admission, 4 h after admission, and 12 h after admission. This study found that lactate did not correlate well with oxygen extraction ratio and that 55% of patients with a lactate of over 2 mmol/L had an oxygen extraction ratio over 30%. This study did note a correlation between lactate and glucose levels.[3] Similarly, Schranz and colleagues did not find a correlation between mixed venous saturation and serum lactate after cardiac surgery in infants.[4]

A few studies have characterised the correlation between lactate and venous saturation in adult populations. While some of these have demonstrated correlation between lactate and adequacy of oxygen delivery, most have demonstrated no correlation. Even those studies demonstrating a correlation only demonstrate a weak correlation.[5,6]

As the body and the component organs require oxygen to function, it seems logical that monitoring systemic oxygen delivery would be important.[7,8] Systemic oxygen delivery is the product of cardiac output and oxygen content. Cardiac output is quantified by the Fick principle as the quotient of oxygen consumption and the arteriovenous oxygen content difference. Oxygen content is a function of haemoglobin, saturation, and the partial pressure of oxygen. Other than arterial saturation, other continuously, noninvasively monitored haemodynamic variables (heart rate and blood pressure, for example) are not directly related to

https://doi.org/10.1017/S1047951124026805 Published online by Cambridge University Press

systemic oxygen delivery. In fact, in critically ill paediatric patients, the inadequacy of routine monitoring to assess systemic oxygen delivery has been demonstrated.[9]

More invasive metrics used to assess the adequacy of systemic oxygen delivery have been less frequently studied. Lactate is one such metric. Lactate is produced by the body mainly as a product of glycolysis. Under normal conditions, as glucose feeds into the glycolytic pathway, pyruvate is produced to then feed into the Krebs cycle and undergo oxidative phosphorylation. However, under conditions such as low oxygen content or low NAD+ (Nicotinamide Adenine Dinucleotide), lactate is produced to compensate. Lactate can also be produced by the body under normoxic conditions. The now well-studied Warburg effect describes proliferative tissues' production of lactate in favour of pyruvate by means of glycolysis despite the presence of oxygen. While this process is most often thought of in terms of tumour cells, studies have found the Warburg effect to occur in non-malignant processes as well.

Both, venous and arterial lactate levels serve as critical markers in assessing tissue perfusion and cellular oxygenation. In instances of inadequate tissue oxygen delivery or impaired cellular metabolism, such as shock or sepsis, the body's compensatory mechanisms lead to an increase in lactate production.[10–12]

Arterial lactate levels reflect the amount of lactate present in the bloodstream, indicating the balance between lactate production and clearance by the liver and other organs. Elevated arterial lactate levels suggest tissue hypoperfusion and anaerobic metabolism. In contrast, venous lactate levels, typically obtained from central venous or mixed venous blood samples, represent the amount of lactate returning to the heart from the tissues. Venous lactate levels can thus provide insights into the adequacy of tissue oxygenation and the effectiveness of tissue perfusion. Discrepancies between arterial and venous lactate levels may indicate the presence of tissue-specific metabolic abnormalities or regional variations in perfusion. Despite these differences, both arterial and venous lactate levels are valuable and interchangeable in clinical practice as indicators of poor perfusion.[11,13,14] They can guide resuscitative efforts and therapeutic interventions aimed at improving tissue oxygenation and restoring perfusion.

Understanding that lactate can be produced in even normoxic conditions is important as lactate's current role in medicine is often centred on its use as a marker for anaerobic metabolism. Studies have discerned many more functions of lactate throughout the body beyond being a marker, albeit not sensitive or specific, of anerobic metabolism. Lactate plays a role in acute inflammation, chronic inflammation, wound healing, and intracellular signalling among others.[15,16]

While lactate may not correlate with adequacy of oxygen delivery, it should not be denied that it demonstrated prognostic ability. The current study did not investigate the prognostic ability of lactate, but previous studies have done so in paediatric cardiac ICU patients and have demonstrated prognostic ability.[17–24] Adequacy of oxygen delivery, systemic or regional, is best done by either directly measuring an underlying venous saturation or by using a surrogate such as near-infra-red spectroscopy.[8,25,26]

This study is one of few paediatric studies that investigate the correlation between lactate and venous saturation and utilise high-fidelity haemodynamic monitoring data. The use of high-fidelity haemodynamic monitoring data allows for maximisation of data available for the analyses, strengthening power.

Despite the strengths of this study, it is not without its limitation. This is a single centre study so centre specific considerations may impact the findings of this study and thus its generalizability. Some will criticise the low patient number. It is important to note that sample size in such time series analyses is not the patient number but the number of time points. A previous study has, nonetheless, investigated model quality based on patient number and time point number and found that with approximately 35 patients, 8 time points per patient, or a sample size of 280 total data points, results in high model quality.[27] With approximately 6 time points per patient in the current study, there is good model quality. The best correlate of this statistical phenomenon is found in meteorological modelling in which the temperature or precipitation for a specific city is being modelled. The sample size in such an analysis isn't one, the number of cities from which the data is drawn, but rather is the number of time points being used from that city. Further discussion of this phenomenon is beyond the scope of this manuscript although a reference is provided here. Another limitation of our study is the potential variability associated with femoral venous line saturations, which may impact the reliability of the data obtained. Finally, it is important to note the potential confounding effect of hyperglycaemia on lactate levels specially in postsurgical patients. Distinguishing patients with hyperglycaemia from those with hypoperfusion solely based on lactate levels can be challenging, as both conditions may contribute to elevated lactate levels.

Conclusion

Venous lactate does not correlate with venous saturation, cerebral oxygen extraction ratio, or renal oxygen extraction ratio in paediatric patients in the cardiac ICU. Only a weak correlation could be identified once the venous saturation was 70% or lower. Venous lactate does not appear to correlate well with markers of the adequacy of oxygen delivery.

Acknowledgements. None.

Authors contribution. RSL, SF, and EGV contributed to the study conception and design. Material preparation, data collection, and analysis were performed by NC and RSL. The first draft of the manuscript was written by JSF and AK. SF and EGV commented on previous versions of the manuscript. All authors read and approved the final manuscript. Reviewing and editing was done by EGV.

Financial support. This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests. The authors declare that they have no conflict of interest.

Ethical standard. The study has been approved by the appropriate institutional ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Data transparency. All data and materials, as well as software application, support our published claims and comply with field standards.

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https://doi.org/10.1017/S1047951124026805 Published online by Cambridge University Press

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