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# Close correlation between arterial and central venous lactate concentrations of children in shock: A cross-sectional study☆

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ABSTRACT

*Background:* Arterial lactate (aLact) has been widely used to guide therapeutic decisions in children with shock. We evaluated the feasibility of central venous lactate (cvLact) in assessing aLact among children with shock.
*Methods:* Pairs of arterial and central venous samples for lactate concentrations were collected simultaneously during the shock and hemodynamically stable states. The results were analyzed by using a Cobas 8000 analyzer.
*Results:* Sixty-four blood paired samples were collected from 48 patients. The overall correlation between central venous and arterial lactate concentrations was $r = 0.962$, $p < 0.0001$, $r^2 = 0.965$. The regression equation was aLact = (0.978 × cvLact) − 0.137. A similar correlation was found between central venous and arterial lactate concentrations during the states of shock and stable hemodynamics ($r = 0.970$, $p < 0.0001$, $r^2 = 0.966$ and $r = 0.935$, $p < 0.0001$, $r^2 = 0.962$, respectively). The mean difference between central venous and arterial lactate concentrations was 0.20 mmol/l (95% CI: 0.08 to 0.32) and the limits of agreement were − 0.74 mmol/l (95% CI: − 0.94 to − 0.53) and 1.13 (95% CI: 0.93 to 1.34).
*Conclusions:* In situations of shock where a central venous catheter is required, samples from a central vein present an acceptable and timely alternative to arterial samples for quantitating lactate concentrations.

## 1. Introduction

Lactate is a biomarker that has been widely studied and used for many purposes. It can be used in combination with other variables that target hemodynamic end points to guide resuscitation in patients with shock. It also enables risk prediction of severe bacterial infection in the pediatric emergency department [1] and is a prognostic marker for mortality in the pediatric intensive care setting [2,3]. Recently, published data have shown that lower lactate concentrations in the first 12 h are associated with better survival-to-discharge in children who achieve return of spontaneous circulation after cardiac arrest [4]. Despite a lack of robust evidence to support this practice, samples for lactate analysis are traditionally obtained from arterial blood. In developing countries such as Thailand where resource is limited, placement of central venous lines receives greater priority due to its versatility such as fluid resuscitation, vasoactive-inotropic drug administration, as well as monitoring of central venous saturation. Consequently, the current practice in obtaining lactate only after an arterial line is in place has the potential to delay procurement of vital medical information. On the other hand, obtaining lactate samples by arterial puncture in patients without an arterial catheter or the insertion of an arterial catheter require manual skill and are associated with complications [5–7]. In addition, obtaining blood samples from an in situ arterial catheter repeatedly, such as in case of lactate measurements, may increase the risk of infection, thrombosis, or distal embolization. Many studies have reported a good correlation between arterial and central venous or mixed venous lactate concentrations with varying agreements, among critically ill patients including those in shock [8–12]. Most of the participants in those studies have been adults. However we believe this specific body of knowledge to be significant for the pediatric patients since there exists differences between anaerobic enzyme activities in the glycolytic pathway of children vs. adults [13].

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## 2. Materials and methods

This cross-sectional study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University. Eligible subjects included all children admitted with shock to our multidisciplinary pediatric intensive care unit from October 2013 to October 2014. Informed consent was obtained from their legal guardians before collection of lactate samples.

Patients aged 1 month to 18 y were enrolled in the study if they met the criteria for shock and had central venous catheters in place. Shock was defined as systolic blood pressure < 70 mmHg in children aged 1 to 12 month, systolic blood pressure < 70 mmHg + (child's age in y × 2) in children aged 1 to 10 y and systolic blood pressure < 90 mmHg in children > 10 y. Hemodynamic stability was considered achieved if a systolic pressure > 5th percentile for age had been reached and cardiovascular therapy had not been increased during the previous ≥ 2 h. Patients were excluded if they had contraindications to arterial puncture, had undergone three or more attempts at arterial blood collection, or informed consent had been refused.

Blood for measurement of lactate concentrations was drawn from central venous and arterial lines as close to simultaneously as possible. Arterial puncture was performed in patients who did not have an arterial line. The first sample was collected when the patient developed shock and the second sample when hemodynamic stability had been achieved. Arterial and central venous samples were transported to the laboratory within 10 min of obtaining them. The specimens were centrifuged and the plasma was analyzed using a Cobas 8000 c502 analyzer (Roche Diagnostics). The between-run CVs for lactate was 1.83%.

Clinical and other relevant characteristics including age, weight, sex, Pediatric Risk of Mortality (PRISM) score [14], type of shock, comorbid conditions [presence of acute respiratory distress syndrome (ARDS) or acute liver failure], site of central venous catheter, and outcome (mortality) were recorded.

Sample size was calculated using the nQuery Advisor program version 5.0 (Statistical Solutions) based on the possible correlation between central venous lactate (cvLact) and arterial lactate (aLact), in a 2-sided manner, with a significance level of 0.01 and statistical power of 90%. The correlation coefficient used was 0.5, and 0.0 was taken to the null hypothesis correlation. The required number of the samples was 53 pairs. SPSS ver 18 was used for statistical analysis. Data are expressed as percentage (%), mean ± SD, or median and 25% to 75% interquartile range, as appropriate. Wilcoxon signed-rank test was used to compare between central venous and arterial lactate concentrations. Spearman's correlation between cvLact and aLact concentrations was calculated. The coefficient of determination was used to measure the strength of linear correlation. The MedCalc® software program ver 16.4.3 was used to construct Bland–Altman plots and calculate the mean difference, limits of agreement and their 95% confidence intervals (CI) [15].

To determine the clinical significant difference, the reference change value (RCV) or critical difference was calculated using the following equation: $RCV = 2^{0.5} * Z * (CV_A^2 + CV_I^2)^{0.5}$. Analytical coefficient of variation ($CV_A$) of lactate derived from quality control process in our laboratory was 1.83% and intra-individual biological variation ($CV_I$) derived from www.westgard.com/biodatabase1.htm [16] was 27.3%. The probability factor (Z) = 1.96 for 95% probability of a true change in both directions.

## 3. Results

Sixty-four pairs of blood samples (aLact and cvLact) were obtained from the 48 patients who met the inclusion criteria (Fig. 1). The patients' clinical and other relevant characteristics are presented in Table 1. Two sets of samples for quantitation of lactate concentration were drawn from 16 patients during the shock and hemodynamically stable states, whereas only one set of such samples was obtained from each of 23 patients after achieving hemodynamic stability, and only 1 set from the remaining 9 patients during the shock state. Overall, 25 of 64 (39.1%) paired aLact/cvLact samples obtained during shock and 39 of 64 (60.9%) paired aLact/cvLact samples obtained after achieving hemodynamic stability were available for analysis. None of children's samples were tested twice. The median (IQR) lactate values were 2.50 (2.00, 3.95) mmol/l for arterial blood and 2.90 (2.35, 4.25) mmol/l for central venous blood in the shock state and 1.20 (0.80, 2.00) mmol/l for arterial blood and 1.30 (1.00, 2.10) mmol/l for central venous blood in the hemodynamically stable state. Comparison of overall aLact and cvLact concentrations in the presence or absence of co-morbid conditions are presented in Table 2. Although the comparison between aLact and cvLact were statistically significant difference, none of samples had the difference [(aLact − cvLact) * 100 / aLact] exceeding the RCV (RCV = 76%). As shown in Fig. 2, cvLact was highly correlated with aLact over the whole data set ($r = 0.962$, $p < 0.0001$, $r^2 = 0.965$). In linear regression analysis, the regression equation was aLact = (0.978 × cvLact) − 0.137. Likewise, strong correlations were found between central venous and arterial lactate concentrations during the state of shock, as well as hemodynamic stability ($r = 0.970$, $p < 0.0001$, $r^2 = 0.966$ and $r = 0.935$, $p < 0.0001$, $r^2 = 0.962$ respectively).

As shown in Fig. 3, Bland–Altman analysis identified an overall mean difference between cvLact and aLact of 0.20 mmol/l (95% CI: 0.08 to 0.32) and the limits of agreement were − 0.74 mmol/l (95% CI: − 0.94 to − 0.53) and 1.13 (95% CI: 0.93 to 1.34). The slope of regression line was not statistically significant, $p = 0.85$, indicating no proportional bias for cvLact. In 5/64 (7.8%) of sampled pairs, the values fell beyond the boundaries of agreement.

## 4. Discussion

The results of this study suggest that there is a very strong correlation between central venous and arterial lactate concentrations in children with shock, both during the shock state and after hemodynamic stability has been achieved. These findings are consistent with those reported by other authors [8,10,11]. Additionally, we demonstrate a reasonable agreement between lactate concentrations in central venous and arterial samples. On the other hand, it is important to note that most published studies use whole blood lactate measurements, whereas ours use plasma lactate, due to its clinical availability at our institution. As a result, this may account for some discrepancies between our finding and those published. For example, the mean difference of 0.2 is larger than that reported by Reminiac et al. (− 0.07 mmol/l); however, these authors reported wider 95% limits of agreement in adult patients with circulatory and/or respiratory failure [11]. In contrast, the agreement we found is less than that reported by Middleton et al. (mean difference 0.08 mmol/l, 95% limits of agreement − 0.27 to 0.42 mmol/l) in critically ill adult patients with and without shock [17]. However, these differences are acceptable due to very high agreement achieved in our data.

In theory, under physiological stress and severe illness lactate production is increased in tissues such as red blood cells, neurons, striated muscle, cardiac muscle, splanchnic organs (liver and intestines), kidneys, and lungs [18,19]. However, central venous blood does not take into account venous drainage from the splanchnic organs, coronary sinus and lungs. As such, central venous lactate values may not represent lactate from these areas. Previous studies showed that patients with acute lung injury or ARDS have higher lactate concentrations in the arterial samples [20,21]. However, in the present study we found higher lactate concentrations in central venous than in arterial samples, including patients with ARDS and acute liver failure. Similar correlations have also been reported in previous studies [8,10,17]. Because our study is comprised of only a few patients with ARDS or acute liver failure, subgroup analysis would have had insufficient statistical power to accurately determine the real effect of those clinical conditions on