Establishment of a Linear Correlation Model of Central Venous Blood Oxygen Saturation and Lactate in Sepsis

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1. Introduction

Sepsis and septic shock are common and potentially lethal complications of chronic illness and acute organ dysfunction secondary to infection [1, 2]. Sepsis is a leading cause of mortality and critical illness worldwide [3, 4]. The incidence of sepsis and septic shock in adults ranges from 56 to 91 per 100,000 population per year [5]. Short term mortality is 20–30%, reaching up to 50% in patients with septic shock [6]. Despite improvements in sepsis care, there has been neither a significant increase in the incidence of sepsis nor a significant improvement in outcomes between 2009 and 2014 [7]. This is despite efforts to improve methods of identifying and managing sepsis with the aim of reducing mortality [8].

Studies of the critically ill have shown that lactate can be used as a marker of tissue hypoxia [9]. Another marker is central venous oxygen saturation (ScvO2), which is a surrogate marker of oxygenation of venous return and hence oxygen delivery and tissue consumption [10]. The relationship between lactate and ScvO2 has been shown to be complex [11, 12].

As both lactate and ScvO2 are markers of tissue oxygenation [13–16], it was posited that levels of lactate and ScvO2 may be correlated in sepsis and in septic shock. We investigated this in a cohort of patients with sepsis by building a linear correlation model to determine the existence of a correlation between these two markers in sepsis and septic shock.

2. Materials and Methods

2.1 Study population

This was a retrospective study, carried out in the Fujian Medical University teaching hospital. The study was conducted according to the ethical principles for medical research stated in the Helsinki Declaration. The study was approved by the Ethics Committee of the Fujian Provincial Hospital.

Exclusion criteria included pregnancy and patients with advanced tumors or irreversible organ failure.

2.2 Data collection

Sepsis and septic shock were defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [17]. Herein, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg and having a serum lactate level of > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

All patients were admitted to the intensive care unit (ICU). Within 1 hour of arrival, the subclavian vein was catheterised and blood samples were taken from the subclavian vein, as well as from the radial or femoral artery. Arterial blood lactate acid concentration and central venous oxygen saturation were determined using the GEM Premier 3500 system.

Patients were divided into the sepsis group (Group1_1) or...
the septic shock group (Group1_2), according to the Sepsis-3 definitions [17]. Patients were further divided according to outcome, into the survival (Group2_1) or the non-survival group (Group2_2).

2.3 Statistical analyses
Data analyses were conducted with SPSS 26 statistical software package (SPSS, Chicago, IL, USA).

First, we performed a missing value analysis of related variables, using the expectation-maximisation (EM) algorithm and regression. Where the Little’s MCAR test did not reach significance (p = 0.05), those missing values were replaced with the series mean.

Group differences with respect to lactate and ScvO2 were tested. Where data were normally distributed, a two-sample t test was carried out (with p < 0.05 representing statistical significance). Where data were non-normally distributed, non-parametric testing was carried out (p < 0.05).

Correlation analysis was then conducted on the consecutive lactate and ScvO2 data, by the calculation of the Pearson correlation coefficient (with p < 0.05 representing statistical significance) and by linear regression analysis.

3. Results
37 patients within the sepsis population were included in this study. Patients were aged 29 – 86 years (Table 1).

3.1 Missing value analysis
There were no missing values of lactate. Six values of ScvO2 were identified, with a deletion rate of 16.2%. Statistical analysis of missing variables, by EM and regression, yielded a Little’s MCAR test result of p = 0.799, indicating that the missing value is missing completely at random. The series mean was used to replace these missing values.

3.2 Differences between groups
Data from the sepsis and septic shock groups were found to be non-normally distributed. Two independent sample non-parametric tests were carried out, with the finding that lactate concentrations were significantly lower in the sepsis group compared to the shock group (p < 0.05, one-tailed). No differences of ScvO2 saturations were found between groups (p > 0.05, one-tailed) (Fig. 1).

Data from the survival and death groups did not conform to a normal distribution, and as such two independent sample non-parametric tests were carried out. Neither lactate nor ScvO2 levels were found to be significantly different between groups (p > 0.05, one-tailed) (Fig. 2).

3.3 Linear correlation analysis
Linear correlation analysis of all observed lactate and ScvO2 data yielded a Pearson correlation coefficient of r^2 = 0.37 (p < 0.001). Linear regression produced estimates for the slope and intercept of this linear relationship according to the equation y = -3.30x + 77.01 (Fig. 3).

Similar analysis was conducted by subject group. In patients with sepsis, the correlation coefficient of lactate and ScvO2 was non-significant (r^2 = 0, p > 0.05). In the septic shock group, the correlation coefficient of lactate and ScvO2 was r^2 = 0.46 (p = 0.001). The linear equation was y = -4.11x + 82.62 (Fig. 4).

In the survival group, linear correlation analysis between lactate and ScvO2 was non-significant (r^2 = 0.101, p > 0.05). In the death group, the correlation coefficient of lactate and ScvO2 was r^2 = 0.67 (p < 0.01). The linear equation was y = -3.70x + 78.61 (Fig. 5).

4. Discussion
Persistently improving of lactate levels suggests ongoing inadequacy of oxygen delivery. High levels of ScvO2 indicate the impaired of the cellular oxygen utilization and microcirculatory, which suggest a systemic oxygen delivery in excess of oxygen demand. Low levels of ScvO2 suggest inadequate oxygen delivery for metabolic demands.

Lactate, which is the product of anaerobic metabolism, is considered the biomarker of choice for reflecting the presence of tissue hypoxia [18, 19]. Reduction in ScvO2 occurs when oxygen delivery to tissues is reduced and oxygen extraction is increased [20]. Elevated ScvO2 suggests a systemic oxygen...
delivery in excess of oxygen demand, impaired mitochondrial oxygen utilization, and/or microcirculatory shunting. Low ScvO2 values imply inadequate oxygen delivery that fails to meet metabolic demands [21].

Early goal-directed therapy (EGDT) for patients with sepsis and septic shock was first implemented by Rivers et al., based on a landmark single center randomized controlled clinical trial (RCT) in which a 16% mortality reduction was achieved by treatment targeting of ScvO2, MAP, central venous pressure and urine output within the first 6 hours after diagnosis [22]. More recently, three multicenter RCTs showed that EGDT did not confer survival benefit compared with usual care for patients with sepsis and/or septic shock, along with suggestions that it should be excluded from the guideline [23, 24]. Interestingly, none of these trials addressed the utility of ScvO2 as a target for resuscitation of septic shock [12], because half of the included patients had normal ScvO2 at the time of randomization. However, studies have shown that lactate and ScvO2 are independent predictors of mortality [25] and that normalization of either or both biomarkers is associated with improved outcomes in sepsis and septic shock [19, 26]. This is consistent with our findings, which demonstrate a complex relationship between lactate and ScvO2. In the implementation of ScvO2 to assess the balance between tissue oxygen supply and consumption in sepsis, the choice of time point is crucial [11].

The present study is an analysis of the relationship between
lactate and ScvO2 in sepsis patients. To our knowledge it is the first analysis of these two markers after stratifying sepsis cases by severity. This study had several limitations, however. First, it is a single-center study including relatively few patients. Second, this study was cross-sectional, so its ability to infer causality is limited.

5. Conclusion

In sepsis, the correlation between ScvO2 and lactate is not constant. As the disease progresses, the correlation may be dynamic. Therefore, in the resuscitation of sepsis and/or septic shock, changes in central venous blood oxygen saturation need attention.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest relevant to this article.

LIST OF ABBREVIATIONS

ScvO2: Central Venous Oxygen Saturation; MAP: Mean Arterial Pressure; ICU: Intensive Care Unit; EGDT: Early Goal Directed Therapy; RCT: Randomized Controlled Clinical Trial
REFERENCES


