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Prognostic value of central venous oxygen saturation and blood lactate levels measured simultaneously in the same patients with severe systemic inflammatory response syndrome

중증 전신성 염증 반응 증후군 환자에서 혈중 젖산 농도와 중심정맥 산소 포화도의 예후적 가치에 관한 연구

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ABSTRACT

Introduction: Blood lactate levels and central venous oxygen saturation($ScvO_2$) are known to be useful indicators of global tissue hypoxia. However, it is unclear whether $ScvO_2$ correlates with lactate levels when measured simultaneously and whether changes in $ScvO_2$ or lactate levels in serial measurements have prognostic value. We investigated the correlation between $ScvO_2$ and lactate levels measured simultaneously and their association with clinical outcomes

Methods: We performed a prospective observational study of patients with severe systemic inflammatory response syndrome(SIRS) and severe sepsis who were admitted to the medical intensive care unit(ICU). $ScvO_2$ and lactate levels were measured simultaneously at the time of study enrollment, every 6 h for 24 h, and then every 24 h until the goal was reached.

Results: Twenty-five patients were enrolled in the study and 13 had died and 12 had survived. There was no correlation between lactate levels and $ScvO_2$. Neither lactate levels nor $ScvO_2$ at the time of admission differed between non-survivors and survivors. Normalization of lactate levels within 48 h was significantly associated with survival.

Conclusions: In patients with severe SIRS and severe sepsis, simultaneously measured $ScvO_2$ and lactate levels showed no correlation, and normalization of lactate levels within 48 h was a predictive factor for survival

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Keywords: Central venous oxygen saturation (ScvO2), lactate, SIRS, severe sepsis, septic shock

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Introduction

The systemic inflammatory response can progress to severe sepsis, septic shock, and multiorgan failure (1). This progression of systemic inflammatory injury and sepsis leads to circulatory abnormalities and increases metabolic requirements (2). Consequently, a systemic imbalance is created between systemic oxygen delivery and demand, resulting in global tissue hypoxia (3). Global tissue hypoxia contributes to the development of multisystemic organ dysfunction syndrome and increased mortality (4).

The most well-known biomarkers of global tissue hypoxia are low central venous oxygen saturation ($ScvO_2$) and hyperlactatemia (5). $ScvO_2$ has been shown to b8e a surrogate for the cardiac index as a target for hemodynamic therapy. A decreased $ScvO_2$ results from an imbalance between oxygen delivery and oxygen consumption (6). When systemic oxygen delivery decreases, the systemic oxygen extraction ratio increases as a compensatory mechanism to match systemic oxygen demand. This results in a decrease in $ScvO_2$, which reflects global tissue hypoxia. In contrast, high $ScvO_2$ values do not always indicate adequate tissue oxygen delivery.

When oxygen extraction is pathologically impaired because of microcirculatory dysfunction or the inability of cells to use the oxygen, $ScvO_2$ remains high in the presence of hypoxia at the tissue level (8, 9).

Lactate is also a useful and clinically obtainable surrogate marker of tissue hypoxia and disease severity (7). When the limit of this compensatory increase in oxygen extraction (anaerobic threshold) is reached, anaerobic metabolism ensues, leading to lactate production (8). Thus, hyperlactatemia in

critically ill patients has usually been interpreted as a marker of secondary anaerobic metabolism due to an inadequate oxygen supply that induces cellular distress. However, this is not always the case and should not be rigorously interpreted as an indicator of hypoxia (5). In skeletal muscle and other tissues, aerobic glycolysis is linked to Na^+-K^+ ATPase activity and stimulates epinephrine (9, 10). The presence of hyperlactatemia under well-oxygenated conditions can be explained by these findings (11). In addition, lactate concentrations reflect the balance between lactate production and clearance. Liver and kidney functions and their blood flow influence lactate clearance because blood lactate is metabolized mainly by the liver and kidneys (12). Thus, as opposed to $ScvO_2$, which is a rudimentary indicator of only the balance between oxygen supply and demand, blood lactate levels reflect the general homeostasis of the host.

Both $ScvO_2$ and blood lactate levels were used as a goal of early sepsis resuscitation in many studies; however, there remains significant debate regarding the relative value of $ScvO_2$ *vs.* blood lactate levels (13, 14). To our knowledge, no prospective study has directly compared $ScvO_2$ and blood lactate levels measured simultaneously in the same patients with systemic inflammatory response syndrome (SIRS) or sepsis. In this study, we investigated the correlation between $ScvO_2$ and blood lactate levels measured simultaneously in the same patients and compared their prognostic values.

Materials and Methods

Study Design and Patients

A prospective observational study of patients with severe SIRS and severe sepsis was conducted in Seoul National University Hospital, Seoul, Korea from June to September 2012. This study was approved by the local institutional review board for human research and performed in accordance with Good Clinical Practice guidelines (IRB No. H-1204-121-408). SIRS was defined according to the presence of two or more of four criteria for SIRS: (1) temperature of >38°C or <36°C; (2) heart rate of >90 beats per minute; (3) respiratory rate of >20 breaths per minute or $PaCO_2$ of <32 mmHg; and (4) white blood cell count of >12,000/cu.mm, <4,000/cu.mm, or >10% immature (band) forms (1). Severe sepsis was defined as follows: sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities could include but were not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Hypotension was defined as a systolic blood pressure of <90 mmHg or a reduction of ≥40 mmHg from baseline. (1) Patients with a non-infective insult but pathophysiologic changes equivalent to the definitions of severe sepsis were classified as having severe SIRS (6). The following patients were excluded from the study: age of <20 years, pregnancy, an absolute contraindication to chest or neck central venous catheterization, a do-not-resuscitate status, or advance directives restriction implementation of the protocol. All patients were evaluated by an intensive care specialist and were admitted to the intensive care unit (ICU). All patients

underwent central venous catheterization and were managed according to the Surviving Sepsis Campaign Guideline (15). Volume resuscitation using crystalloids or colloids was initiated to achieve a central venous pressure of 8 to 12 mmHg. Vasoactive agents were used to maintain a mean arterial pressure of >65 mmHg. Urine output of >0.5 mL/kg/h also served as a target goal. Patients were intubated and mechanically ventilated as required.

Measurements and Data Collection

Blood lactate levels and $ScvO_2$ were measured simultaneously every 6 h during the first 24 h after enrollment and then every 24 h until the goals were reached or patients died. The $ScvO_2$ and lactate goal achievements were defined as ≥70% and a lactate plasma or serum level of ≤4 mmol/L, respectively. All patients underwent placement of a chest or neck central venous catheter capable of measuring central venous oxygen saturation. $ScvO_2$ was measured by intermittent sampling, and lactate levels were measured in arterial blood using the hospital's central laboratory.

Data on patient demographics, hemodynamic variables, laboratory values, comorbidities, and admission diagnosis were collected at baseline. Biochemical and clinical variables required for calculation of the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were collected at 0, 6, 12, 18, 24, 48, and 72 h after the start of the study. Therapeutic interventions, such as antibiotics, fluids, packed red cell transfusions, vasoactive agents, and mechanical ventilation given in the ICU and for up to 72 h were recorded.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. For the purpose of this study, blood lactate levels, $ScvO_2$, and organ dysfunction scores (SOFA) were analyzed for all patients enrolled in the study. Descriptive statistics were used to summarize patient characteristics. To investigate the correlation among blood lactate levels, $ScvO_2$, and SOFA scores that were measured simultaneously, we estimated the correlation coefficient between two variables with repeated observations using a mixed-effects model. A correlation analysis was employed between blood lactate levels and $ScvO_2$, which were measured simultaneously in one patient. Mixed models were used to estimate the differences in lactate levels and $ScvO_2$ between survivors and non-survivors. We evaluated the concordance rate of reaching the $ScvO_2$ and lactate goals using Cohen's kappa. Logistic regression using generalized estimation equations was performed to evaluate the association of clinical outcomes according to the achievement of goals. Data are presented as percentages or means ± standard deviation.

Results

Baseline Characteristics of Patients

Twenty-five patients were included in the study. Their mean age was 68.12 ± 13.6 years, and 18 patients (72%) were male. About 50% of patients had comorbidities, specifically hypertension or malignancy. Patients had a mean baseline APACHE II score of 33.72 ± 8.0 and SOFA score of 12.32 ± 4.6 at the time of admission to the ICU. A total of 96% of patients required mechanical ventilation, and continuous renal replacement therapy was applied in 68% of patients (Table 1).

Among 25 patients, 4 patients were from non-specific insult, 10 patients had the documented infection, and 11 patients were presumed to have infectious process. As sepsis is defined as SIRS with a presumed or a confirmed infectious process, 21 patients were severe sepsis. Among 10 patients with documented infection, blood cultures revealed bacteria in 5 patients and fungi in 2 patients. Bacteria were isolated from sputum, ascites and wound in 3 patients.

Table 1. Baseline characteristics of patients

Variable	Total (n=25)
Age (years), mean ± SD	68.12 ± 13.6
Male sex (%)	18 (72%)
Comorbidities (%)	
Diabetes mellitus	9 (36%)

Hypertension	13 (52%)
COPD	3 (12%)
ESRD	4 (16%)
Malignancy	12 (48%)
Disease severity	
APACHE II score	33.72 ± 8.0
SOFA score	12.32 ± 4.6
Intervention	
Mechanical ventilation	24 (96%)
Continuous renal replacement therapy	17 (68%)
Norepinephrine administration	18 (72%)

SD = Standard deviation; COPD = Chronic obstructive pulmonary disease; ESRD = end stage renal disease; APACHE II = Acute physiology and chronic health evaluation; SOFA = Sequential organ failure assessment; CRRT = Continuous renal replacement therapy

Correlation Between $ScvO_2$ and Blood Lactate Level and Their Relationship with SOFA Score

A statistically significant correlation was not observed between $ScvO_2$ and blood lactate levels (correlation coefficient, 0.0504; $p > 0.05$). $ScvO_2$ showed no correlation with SOFA scores (correlation coefficient, 0.0218; $p > 0.05$). In contrast, blood lactate levels revealed a positive correlation with SOFA scores (correlation coefficient, 0.571; $p < 0.05$). (Table 2)

Table 2. Correlation analysis among $ScvO_2$, blood lactate level, and SOFA score.

Variable	Correlation coefficient
$ScvO_2$ and lactate	0.0504
$ScvO_2$ and SOFA score	0.0218
Lactate and SOFA score	0.5710

SOFA = Sequential organ failure assessment; ScvO2 = central venous oxygen saturation

Concordance rate of reaching $ScvO_2$ and lactate goals within 24h

Ten patients met the $ScvO_2$ goal and 15 met the lactate goal. Of the 10 patients who met the $ScvO_2$ goal, 7 met the lactate goal and 3 did not reach the lactate goal.(Table 3)

Table 3. Concordance rate of reaching $ScvO_2$ and lactate goals.

	Met lactate goal	Did not meet lactate goal	Total
Met $ScvO_2$ goal	7	3	10
Did not meet $ScvO_2$ goal	8	6	14
Total	15	9	24

Of the 14 patients who did not meet the $ScvO_2$ goal, 8 met the lactate goal and 6 did not reach the lactate goal. There was no statistically significant agreement between the $ScvO_2$ and lactate goal achievements (k = 0.12, 95% CI = 0.668–0.686).

Association of reaching $ScvO_2$ and blood lactate goals with clinical outcomes

Among the 25 patients, 13 had died and 12 had survived at the end of the measurements. We evaluated whether there was a difference in the clinical characteristics between survivors and non-survivors. There was no significant difference between the groups in any of the baseline characteristics, with the exception of the disease severity score (Table 4).

Table 4. Baseline characteristics of survivors and non-survivors.

Variable	Survivors (n = 12)	Non-survivors (n = 13)	*P* value
Age (yrs), mean± SD	69.3 ± 13.7	67 ± 14.1	0.679
Male sex (%)	9 (75%)	9 (69.2%)	0.760
Comorbidities (%)			
Diabetes mellitus	4 (33.3%)	5 (38.5%)	0.800
Hypertension	7 (58.3%)	6 (46.2%)	0.562
COPD	2 (16.7%)	1 (7.7%)	0.511
ESRD	1 (8.3%)	3 (23.1%)	0.336
Malignancy	5 (41.7%)	7 (53.6%)	0.511
Disease severity			
APACHE II score	27.92 ± 5.3	39.08 ± 6.2	0.000
SOFA score	9.42 ± 4.1	15 ± 3.2	0.001
Intervention			
Mechanical ventilation	11 (91.7%)	13 (100%)	0.337

Continuous renal replacement therapy	6 (50%)	11 (84.6%)	0.074
Norepinephrine administration	5 (41.7%)	13 (100%)	0.002

SD = Standard deviation; COPD = Chronic obstructive pulmonary disease; ESRD = end stage renal disease; APACHE II = Acute physiology and chronic health evaluation; SOFA = Sequential organ failure assessment; CRRT = Continuous renal replacement therapy

Next, the $ScvO_2$ and blood lactate levels at the time of ICU admission were compared between survivors and non-survivors. There was no statistically significant difference between survivors and non-survivors in blood lactate levels (3.01 *vs.* 5.45 mmol/L, respectively; $p = 0.062$) or $ScvO_2$ (65.9% *vs.* 66.3%, respectively; $p = 0.951$) at the time of enrollment. Interestingly, the serial blood lactate measurements, but not $ScvO_2$ ($p = 0.4566$), showed a significant difference between survivors and non-survivors ($p = 0.0043$). The blood lactate levels of non-survivors at 6, 12, 24, and 48 h after admission to the ICU were higher than those of survivors at 6, 12, 24, and 48 h ($p < 0.05$) (Table 5).

Table 5. Comparison of $ScvO_2$ and blood lactate levels between survivors and non-survivors.

Variable	Survivors (n = 12)	Non-survivors (n = 13)	*P* value
Lactate			
Initial	3.01 ± 2.34	5.45 ± 3.65	0.062

6 h	2.91 ± 2.23	6.62 ± 4.92	0.025
12 h	2.85 ± 2.46	8.27 ± 6.03	0.009
24 h	3.27 ± 2.45	7.87 ± 5.30	0.015
48 h	2.42 ± 1.92	7.68 ± 5.30	0.006
$ScvO_2$			
Initial	65.91 ± 14.05	66.30 ± 16.45	0.951
6 h	66.19 ± 8.22	72.75 ± 15.59	0.207
12 h	72.93 ± 9.43	70.90 ± 12.23	0.649
24 h	70.45 ± 13.26	70.69 ± 8.07	0.959
48 h	65.97 ± 15.18	72.94 ± 11.40	0.217

ScvO2 = central venous oxygen saturation; h = hour

We next evaluated the association between clinical outcomes and the achievement of goals by logistic regression analysis. Normalization of blood lactate levels (≤4 mmol/L) within 24 or 48 h was significantly associated with survival (Table 6).

Table 6. Associations between mortality and the achievement of ScvO2 or blood lactate goals by logistic regression analysis.

Variable		OR (95% CI)	*P* value
Lactate			
6 h	Normalized	1	
	Not normalized	5.833 (0.900-37.818)	0.0644
12 h	Normalized	1	
	Not normalized	5.833 (0.900-37.818)	0.0644
24 h	Normalized	1	

	Not normalized	10.000 (1.444–69.259)	0.0197
48 h	Normalized	1	
	Not normalized	22.000 (2.050–236.054)	0.0107
$ScvO_2$			
6 h	Normalized	1	
	Not normalized	0.857 (0.178–4.126)	0.8476
12 h	Normalized	1	
	Not normalized	0.857 (0.178–4.126)	0.8476
24 h	Normalized	1	
	Not normalized	1.000 (0.202–4.955)	1.000
48 h	Normalized	1	
	Not normalized	0.714 (0.143–3.579)	0.6824

ScvO2 = central venous oxygen saturation; h = hour; OR = odds ratio; CI = confidence interval

In contrast, normalization of $ScvO_2$ (>70%) was not significantly correlated with survival. In multivariate logistic regression analysis using statistically significant univariate variables associated with mortality, lactate normalization within 48 h was statistically significantly associated with mortality (OR, 22; $p = 0.0107$).

Discussion

Severe SIRS or sepsis evolves as a series of hemodynamic phases in which $ScvO_2$ and lactate can serve as surrogates for monitoring the balance between systemic oxygen delivery and demands and for quantifying the severity of global tissue hypoxia (5, 16). In a state of global tissue hypoxia, a decreased $ScvO_2$ is likely to precede the appearance of lactate. However, which parameter reflects the tissue hypoxia more accurately is unclear. Both $ScvO_2$ and blood lactate levels were used as a goal of early sepsis resuscitation in many studies. Although the optimal goal of resuscitation of sepsis remains unclear, protocols using $ScvO_2$ as an early quantitative resuscitation goal have been demonstrated to improve outcomes in patients with severe sepsis and septic shock (17). In addition, lactate clearance has been shown to be non-inferior to $ScvO_2$ as the final goal during sepsis resuscitation (18). Considering the underlying physiology and results of studies on resuscitation goals, $ScvO_2$ and blood lactate levels are likely to correlate with each other. However, the specific correlation between them is unclear. In many previous studies, the $ScvO_2$ and blood lactate levels were not measured simultaneously in the same patient, which is necessary to assess their correlation. In this study, we measured the $ScvO_2$ and blood lactate levels simultaneously in the same patient to evaluate the correlation between them. Unexpectedly, there was no correlation between the $ScvO_2$ and blood lactate levels in the same patient. This suggests that each of these physiological processes is complex and influenced by multiple factors. $ScvO_2$ has a half-life of only seconds and

provides immediate feedback regarding the relationship between oxygen delivery and consumption, which depends on the phase of sepsis (19). A low $ScvO_2$ does not always reflect tissue hypoxia. In addition, a normal $ScvO_2$ cannot exclude the possibility of tissue hypoxia. In sepsis, the $ScvO_2$ may be elevated despite tissue hypoxia, perhaps secondary to maldistribution of flow. This leads to concerns that the $ScvO_2$ may not always be a reliable target for quantitative resuscitation because it can sometimes be normal to elevated despite evidence of significant tissue hypoxia (8, 20). Compared with $ScvO_2$, lactate is a delayed indicator of tissue perfusion and has complex kinetics (21). Elevated blood lactate has long been regarded as a marker of anaerobic metabolism. However, aerobic mechanisms—such as cytokine-mediated glucose uptake and catecholamine-stimulated Na-K pump overactivity—can lead to lactate production in patients with sepsis. Although the blood lactate level usually increases when tissue hypoxia is present, a normal blood lactate level does not exclude the presence of tissue hypoxia. An elevated blood lactate level was not observed in 20% to 50% of patients with septic shock at presentation or during the clinical course. All of these findings suggest that neither $ScvO_2$ nor hyperlactatemia always reflect tissue hypoxia because they are affected by many confounding factors. Different confounding factors could give rise to a lack of correlation between $ScvO_2$ and blood lactate levels. This is supported by the absence of significant concordance in achieving $ScvO_2$ and lactic acid goals in this study. It is also in accordance with previous reports (22).

In this study, only lactate levels showed statistically significant differences between survivors and non-survivors. In a previous prospective observational

study, oxygen-derived variables showed no significant differences, while blood lactate levels had a strong relationship with survival (23). Many studies have shown that lactate clearance, as a target of resuscitation, predicts better survival (24, 25). There were no significant differences in $ScvO_2$ between survivors and non-survivors at any measurement point in this study; in contrast, many studies have suggested that low $ScvO_2$ is a good predictor of a poor prognosis (17, 26).

What is the reason for this difference? The major difference between this and previous studies is the method of $ScvO_2$ measurement. While we measured $ScvO_2$ intermittently by sampling at designated times, $ScvO_2$ was measured by continuous monitoring in previous studies. Continuous $ScvO_2$ monitoring, which provides a real-time assessment, has been suggested to be superior to intermittent monitoring (20). However, it requires special equipment, such as a continuous central venous oxygen spectrophotometer and an appropriate central venous catheter. This is a major barrier that limits its generalizability. Thus, the intermittent monitoring of $ScvO_2$ used in this study might reflect the real practice in the majority of ICUs. The lack of real-time assessment of $ScvO_2$ might be the reason for the failure of $ScvO_2$ to show prognostic significance in this study. In a recent prospective observational pilot study, intermittent $ScvO_2$ monitoring was not inferior to continuous $ScvO_2$ monitoring when delivered within the first 6 h of intervention (27). However, another study comparing $ScvO_2$ measurements showed that the achievement of goals and survival were improved to a greater degree with continuous observation of $ScvO_2$ (28). To validate intermittent monitoring of $ScvO_2$, a large randomized multicenter study is needed.

All of our measurements and comparisons of $ScvO_2$ and lactate levels were obtained after ICU admission, while patients in previous studies were enrolled and monitored at emergency departments. Guidelines for management of severe sepsis and septic shock recommend that the initial resuscitation goal is achieved during the first 6 h of resuscitation (29). This is based on early goal-directed therapy and emphasizes initial resuscitation. The present study's enrollment time may be a limitation to the interpretation of our results in terms of the fact that it may not reflect the critical time of early sepsis resuscitation in some patients. In addition, our study is limited in its clinical application in that it was designed as an observational study without intervention and involved a small sample size. The failure to demonstrate prognostic significance of initial lactate or ScvO2 in this study could be due to either missing earlier data or small sample size. These limitations should be noted when interpreting the study results and warrants further studies in this area.

In conclusion, simultaneously measured blood lactate and $ScvO_2$ show no correlation in patients with severe sepsis and septic shock, and blood lactate levels, but not $ScvO_2$, are associated with patient prognosis.

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초 록

서론: 전신성 염증 반응 증후군환자에서 순환부전과 산소요구량의 증가로 적절한 조직 대사요구량을 충족시키지 못함으로 인하여 조직 저산소증이 발생한다. 이에 조직 저산소증의 지표로 젖산농도와 중심정맥 산소포화도가 유용하다고 알려져 있으며 본 연구에서는 이러한 지표들의 변화와 환자의 임상경과를 관찰하여 연관성을 알아보고자 하였다

방법: 전향적 관찰 연구로 2012 년 3 월부터 서울대학교병원 내과계중환자실에 입실한 중증 전신성 염증 반응 증후군환자 중 입실 당시 중심정맥 산소포화도 70% 이하이거나 젖산농도가 2mmol/L 이상인 환자를 대상으로 입실 당일에는 6 시간, 그 후에는 24 시간 간격으로 중심정맥 산소 포화도와, 젖산농도를 동시에 측정하였다. 이와 함께 환자의 기저 상태, 입실 당시 및 입실 기간 중의 생리적 지표 및 중증도 지표를 수집하였다

결과: 25 명의 환자가 연구에 포함되었고 이 중 13 명의 환자가 사망하였으며 12 명의 환자가 중환자실 퇴실 당시까지 생존하였다. 동일한 시간에 측정한 두 지표의 분포는 연관성을 보이지 않았다. 입실 당시의 젖산농도와 중심정맥 산소 포화도는 사망군과 생존군에서 모두 통계적으로 유의한 차이를 보지 않았다. 사망을 예측하는 지표로 48 시간이내 젖산농도 4mmol/L 이하에 도달한 경우에 유의한 결과를 보였다.

결론: 중증 전신성 염증 증후군 환자에서 동시에 측정한 혈중 젖산농도와 중심정맥 산소 포화도는 연관성을 보이지 않았으며, 젖산농도의 정상화 여부가 예후와 관련이 있는 것으로 생각된다.

주요어 : 중심정맥 산소 포화도, 젖산, 전신성 염증 증후군

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