Value of combined lactate and central venous oxygen saturation measurement in patients with sepsis: a retrospective cohort study

K. Sitthikool, J.H. Boyd, J.A. Russell, K.R. Walley

St. Paul's Hospital, The University of British Columbia, Vancouver, BC, Canada

Abstract

Introduction. Lactate and central venous oxygen saturation ($ScvO_2$) reflect tissue hypoperfusion but each measure is confounded by many additional factors. These confounding factors differ between lactate and $ScvO_2$. ***Objectives***. We postulated that combined assessment of lactate and $ScvO_2$ may yield information beyond that of each measure alone. Specifically we sought to determine whether lactate has different characteristics and predictive value at different levels of $ScvO_2$. ***Material and methods***. We conducted a retrospective analysis of a Derivation cohort and a Validation Cohort of sepsis patients with lactate and $ScvO_2$ measured within the first 4 hours of intensive care unit admission and 12 hours after resuscitation. Patients were grouped according to: 1) $ScvO_2$ < 60 %; 2) 60 % ≤ $ScvO_2$ < 80 %; 3) $ScvO_2$ ≥ 80 %. ***Results***. Lactate was negatively correlated with $ScvO_2$ in the $ScvO_2$ < 60 % group in both cohorts but was not correlated with $ScvO_2$ in the other $ScvO_2$ groups. Using receiver operator characteristic analysis in the Derivation Cohort, in the $ScvO_2$ ≥ 80 % group lactate was predictive of 28-day mortality with an area under the ROC curve (AUC) of 0.94 and an optimal threshold lactate of 3.0 mmol/L. Using this threshold in the $ScvO_2$ ≥ 80 % groups, 28-day mortality was 32.7 %. ***Conclusions***. Lactate has different characteristics and predictive value at different levels of $ScvO_2$. When $ScvO_2$ < 60 % correlation between lactate and $ScvO_2$ is consistent with a degree of oxygen supply limitation. When $ScvO_2$ ≥ 80 % lactate > 3.0 mmol/L is predictive of mortality.

Keywords: central venous oxygen saturation, oximetry, lactate, sepsis, septic shock, prognosis, mortality

Прогностическое значение комбинации уровня лактата и центральной венозной сатурации кислорода у пациентов с сепсисом: ретроспективное когортное исследование

К. Ситтикул, Дж.Х. Бойд, Дж.А. Рассел, К.Р. Велли

Госпиталь Св. Павла, Университет Британской Колумбии, Ванкувер, Канада

Реферат

Актуальность. Уровень лактата и центральная венозная сатурация крови ($ScvO_2$) отражают гипоперфузию тканей, но на каждый показатель влияет множество дополнительных факторов. Эти дополнительные факторы различны для лактата и $ScvO_2$. ***Цель исследования***. Мы предполагаем, что одновременная оценка уровня лактата и $ScvO_2$ может дать более ценную информацию, чем измерения показателей по отдельности. В частности, мы стремились определить, обладает ли лактат различными характеристиками и различной прогностической ценностью при разных уровнях $ScvO_2$. ***Материал и методы***. Мы провели ретроспективный анализ экспериментальной и контрольной когорты пациентов с сепсисом, у которых уровень лактата и $ScvO_2$ измеряли в течение первых 4 ч после поступления в ОИТ и через 12 ч после реанимации. Пациенты были сгруппированы по критериям: 1) $ScvO_2$ < 60 %; 2) 60 % ≤$ScvO_2$ < 80 %; 3) $ScvO_2$ ≥ 80 %. ***Результаты***. Уровень лактата отрицательно коррелировал с $ScvO_2$ в группе $ScvO_2$ < 60 % в обеих когортах, но в других группах $ScvO_2$ корреляции выявлено не было. Используя анализ ROC-кривых в экспериментальной когорте, установлено, что в группе $ScvO_2$ ≥ 80 % уровень лактата прогнозировал 28-дневную смертность с площадью под кривой 0,94 и оптимальным пороговым значением лактата 3,0 ммоль/л. С учетом этого порога 28-дневная смертность в группе $ScvO_2$ ≥ 80 % составила 32,7 %.

© **«Практическая медицина» 2021.** Данная статья распространяется на условиях «открытого доступа», в соответствии с лицензией. CC BY-NC-SA 4.0 («Attribution-NonCommercial-ShareAlike» / «Атрибуция-Некоммерчески-СохранениеУсловий» 4.0), которая разрешает неограниченное некоммерческое использование, распространение и воспроизведение на любом носителе при условии указания автора и источника. Чтобы ознакомиться с полными условиями данной лицензии на русском языке, посетите сайт: https://creativecommons.org/licenses/by-nc-sa/4.0/deed.ru

✉ *For correspondence:* Keith R. Walley — MD, Professor, Critical Care Medicine, St. Paul's Hospital, The University of British Columbia, Vancouver, Canada; e-mail: Keith.Walley@hli.ubc.ca

For citation: Sitthikool K., Boyd J.H., Russell J.A., Walley K.R. Value of combined lactate and central venous oxygen saturation measurement in patients with sepsis: a retrospective cohort study. Annals of Critical Care. 2021;4:59–68. DOI: 10.21320/1818-474X-2021-4-59-68

Received: 07.10.2021
Accepted: 30.11.2021
Дата онлайн-публикации: 19.01.2022

Заключение. Уровень лактата имеет разные характеристики и прогностическую ценность при разных уровнях $ScvO_2$. При $ScvO_2$ < 60 % корреляция между уровнем лактата и $ScvO_2$ связана со степенью гипоксии. В группе $ScvO_2$ ≥ 80 % уровень лактата > 3,0 ммоль/л является прогностическим фактором смертности.

***Ключевые слова*:** центральная венозная сатурация кислорода, оксиметрия, лактат, сепсис, септический шок, прогнозирование, смертность

✉ *Для корреспонденции:* Кит Р. Велли — д-р медицины, профессор, отдел критической медицины, Больница Святого Павла, Университет Британской Колумбии, Ванкувер, Канада; e-mail: Keith.Walley@hli.ubc.ca

Для цитирования: Ситтикул К., Бойд Дж.Х., Рассел Дж.А., Велли К.Р. Прогностическое значение комбинации уровня лактата и центральной венозной сатурации кислорода у пациентов с сепсисом: ретроспективное когортное исследование. Вестник интенсивной терапии им. А.И. Салтанова. 2021;4:59–68. DOI: 10.21320/1818-474X-2021-4-59-68

Поступила: 07.10.2021
Принята к печати: 30.11.2021
Published online: 19.01.2022

DOI: 10.21320/1818-474X-2021-4-59-68

Introduction

Current guidelines suggest "guiding resuscitation of sepsis and septic shock to decrease lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion" [1]. Earlier guidelines suggested using central venous oxygen saturation ($ScvO_2$) to guide resuscitation of sepsis and septic shock. Yet both lactate and central venous oxygen saturation are highly confounded by factors other than tissue hypoperfusion [2–4] although both share tissue hypoperfusion as one of their underlying determinants. We therefore postulated that the combination of lactate and $ScvO_2$ would provide additional information beyond the individual measurement of lactate or $ScvO_2$.

Lactic acidemia is a biomarker of tissue hypoxia [8–9] and is associated with adverse outcome [9–12]. Regional ischemia (e.g. gut, limb) must be distinguished from inadequate whole body oxygen delivery as the cause of elevated lactate. In the absence or regional ischemia, elevated lactate levels may also be due to accelerated glycolysis driven by sepsis or beta-adrenergic stimulation, reduced entry of pyruvate into the Kreb's cycle due to thiamine deficiency or other causes, increased conversion of pyruvate to lactate in a reducing environment or, not infrequently, due to decreased lactate clearance due to hepatic dysfunction or other causes. The Hour-1 Surviving Sepsis Campaign Bundle of Care recommends measuring a lactate level. If the initial lactate level is more than 2 mmol/L, it should be re-measured [13]. Previous studies suggest a significant reduction in mortality with "lactate-guided" resuscitation [14–15]. However, these conclusions are clouded because, in a key open-label randomized-controlled trial of early lactate-guided therapy, the treatment algorithm also involved interventions guided by $ScvO_2$ [14].

Mixed venous oxygen saturation (SvO_2) and its surrogate, $ScvO_2$ measured from a thoracic central line [16], can be used to evaluate oxygen supply/demand adequacy [17] and estimate cardiac output using the Fick equation [18]. Low $ScvO_2$ helps identify inadequate oxygen delivery conditions [17]. High $ScvO_2$ generally indicates adequate oxygen delivery but, importantly, this is not always the case. For example, $ScvO_2$ may be paradoxically high when tissue oxygen extraction is pathologically impaired due to cellular dysfunction involving mitochondria, cofactors, antioxidants, or membrane stabilizers [19]. Early Goal-Directed Therapy targeting $ScvO_2$ as part of the initial resuscitation of septic shock improved outcomes in an early study [20] but failed to improve outcomes in later studies [21–24]. The latter studies are clouded because both the intervention and control groups had already received protocolized initial fluid resuscitation; a key component

of Early Goal-Directed Therapy, which was the treatment to be tested.

Thus, lactate and $ScvO_2$ both reflect tissue hypoperfusion but each measure is confounded by many additional factors that have not been fully addressed in any study. Importantly, the confounding factors differ between lactate and $ScvO_2$. Thus, it is possible that combined assessment of lactate and $ScvO_2$ may yield information beyond that of each measure alone. Accordingly, we explored the relationship between combined lactate and $ScvO_2$ measurements and clinical outcomes. Specifically, we sought to determine whether serum lactate concentration has different characteristics and predictive value at different levels of central venous oxygen saturation ($ScvO_2$).

Materials and Methods

Patient cohorts

Derivation Cohort. All patients admitted to the Intensive Care Unit at St Paul's Hospital (SPH) in Vancouver, British Columbia, Canada, between 2004–2009 were screened for sepsis (n = 754). Sepsis was defined by an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points due to infection [25]. Of these, 274 patients who had lactate and $ScvO_2$ measurements within the first 4 hours of study enrollment were included in this analysis as a Derivation Cohort. The study was approved by the University of British Columbia Research Ethics Board (H02-50076-A027).

Validation Cohort. To reduce the possibility of false positive results from the Derivation Cohort we tested for replication of findings in a Validation Cohort. All patients admitted to the Intensive Care Unit at SPH from 2010 to 2018 were screened for sepsis (n = 855). Sepsis was defined using the same consensus definition as above [25]. Of these, 289 patients had lactate and $ScvO_2$ measurements within 4 hours of study enrollment. The study was approved by the University of British Columbia Research Ethics Board (H02-50076-A027).

Measurements in both cohorts. Baseline characteristics and medical comorbidities were assessed at the time of enrollment. Laboratory variables (lactate, $ScvO_2$, hemoglobin, white blood cell count, platelet count, alanine aminotransferase, total bilirubin, creatinine) were measured. Previous studies have used 60 % as a cutoff value for a low $ScvO_2$ and 80 % as a cutoff value for a high $ScvO_2$ [26–27]. Therefore, we classified patients into three groups according to $ScvO_2$ measured within the first 4 hours: 1) $ScvO_2$ < 60 %; 2) 60 %≤$ScvO_2$ < 80 %; 3) $ScvO_2$ ≥ 80 %.

Statistical analysis

Median (interquartile range) was employed for continuous variables and percentage was used for categorical variables. Chi square tests were utilized for comparison between groups of categorical variables. Kruskal-Wallis tests were used for non-normally distributed continuous data and ANOVA was used for normally distributed continuous data. Group differences associated with a p-value of ≤ 0.05 were considered statistically significant. A linear regression analysis was used to assess the correlation of $ScvO_2$ and lactate. The receiver operator characteristic (ROC) curve with area under the ROC curve (AUC) was used to derived an optimal lactate threshold predictive of 28-day mortality in the Derivation Cohort. This lactate threshold was then tested for prognostic value in the combined cohorts. Statistical analysis was performed using SPSS Version 23 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

The Derivation Cohort was comprised of 274 sepsis patients having both lactate and $ScvO_2$ measurements within 4 hours of study enrollment. Baseline characteristics are shown in Table 1 A classified by $ScvO_2$ at time of enrollment: 1) $ScvO_2$ < 60 %; 2) 60 % ≤ $ScvO_2$ < 80 %; 3) $ScvO_2$ ≥ 80 %. Patients in the $ScvO_2$ < 60 % group had significantly higher baseline lactate levels (2.5 mmol/L) compared with the other groups ($ScvO_2$ ≥ 60 and < 80 % lactate 1.7 mmol/L; $ScvO_2$ ≥ 80 % lactate 1.3 mmol/L, p = 0.01). Patients having $ScvO_2$ ≥ 80 % were younger (p = 0.02) and had significantly higher creatinine concentrations (p = 0.04). Sex, comorbidities, APACHE II score, and other laboratory measurements at presentation were not different between the three groups. There was no significant difference in primary infection sites of sepsis (Table 1 A).

The Validation Cohort was similarly defined and was comprised of 289 sepsis patients. Patients in the $ScvO_2$ < 60 % group had a higher prevalence of ischemic heart disease and had a higher lactate level point estimate, although not statistically significantly higher (Table 1 B). As in the Derivation Cohort, patients having $ScvO_2$ ≥ 80 % were younger (p = 0.04). Again, sex, comorbidities, APACHE II score, and other laboratory measurements at presentation were not different between the three groups. Similarly, primary infection sites were not different between groups (Table 1, B).

IQR is Interquartile range. APACHE II score is Acute physiology and chronic health evaluation II score.

Table 1. Baseline characteristic in two cohorts of sepsis patients

A:

Variable	Derivation Cohort			*p*
	$ScvO_2$ < 60 % (*n* = 38)	ScvO2 60–80 % (*n* = 172)	$ScvO_2$ > 80 % (*n* = 64)	
Age, yr, median (IQR)	66.9 (48.7–76.1)	60.4 (48.5–69.8)	56.6 (42.1–68.6)	0.02
Male, *n* (%)	22 (57.9)	113 (65.7)	44 (68.8)	0.81
Comorbidities, *n* (%)				
Cirrhosis	0 (0)	4 (2.3)	1 (1.6)	0.61
Other liver disease	3 (7.9)	19 (11.0)	8 (12.5)	0.77
Chronic renal failure	4 (11.1)	23 (13.9)	7 (12.1)	0.87
Hypertension	5 (13.2)	19 (11)	2 (3.1)	0.13
Ischemic heart disease	3 (7.9)	13 (7.6)	8 (12.5)	0.48
Diabetes	1 (2.6)	12 (7.0)	1 (1.6)	0.4
Chronic obstructive pulmonary disease	4 (10.5)	20 (11.6)	3 (4.7)	0.28
APACHE II score, median (IQR)	23 (16–30)	22 (18–27)	24 (19–27)	0.36
Laboratory variables, median (IQR)				
Baseline lactate (mmol/L)	2.5 (1.5–5.1)	1.7 (1.1–4)	1.3 (1–3)	0.01
Baseline $ScvO_2$ (%)	53 (47–57)	72 (67–76)	84 (82–88)	<0.001
Creatinine, µmol/L	126 (80.5–202.5)	128.5 (74–234)	210 (93–362)	0.04
White blood cell count, × 10^3 µL	13.9 (6.8–19.5)	11.6 (5.7–17.7)	11.2 (6.4–16.5)	0.54
Hemoglobin, g/L	99.5 (83–113)	98 (83.5–119.5)	101 (82.5–116.5)	0.77
Platelet count, × 10^3 µL	196.5 (146–252)	153.5 (73.5–209)	165 (88.5–231.5)	0.2
Total bilirubin, µmol/L	12 (9–15.5)	14 (6–32.5)	15 (7–29)	0.62
Alanine aminotransferease, u//L	50.5 (31–125)	37 (22–74)	33 (16–86)	0.18
Infection sites, *n* (%)				
Lung	24 (63.2)	100 (62.5)	36 (56.3)	0.99
Genitourinary	1 (2.6)	3 (1.7)	1 (1.6)	0.3
Abdominal	4 (10.5)	19 (11)	11 (17.2)	0.62
Skin and soft tissue	1 (2.6)	8 (4.7)	2 (3.1)	0.95
Others (central venous system, bone, blood)	2 (5.2)	11 (6.3)	3 (4.7)	0.1

$ScvO_2$ is correlated with serum lactate only when $ScvO_2$ < 60 %

In the Derivation cohort we observed a correlation between higher serum lactate at lower $ScvO_2$ (p = 0.01) in the $ScvO_2$ < 60 % group (Table 2). This negative correlation replicated in the Validation Cohort for the $ScvO_2$ < 60 % group (p = 0.004) (Table 2) suggesting that this finding was not a false positive result. In contrast, no correlation was observed in either the Derivation or Validation Cohorts between lactate levels and $ScvO_2$ for patients in the 60 %≤$ScvO_2$ < 80 % group nor in the $ScvO_2$ ≥ 80 % group (Table 2). Thus, lactate arising from global inadequate oxygen delivery is only evident when $ScvO_2$ < 60 %.

Lactate predicts mortality only when $ScvO_2$ ≥ 80 %

In the Derivation Cohort, lactate was not predictive of 28-day mortality in the $ScvO_2$ < 60 % group (AUC = 0.64, 95 % confidence interval [95% CI], 0.40–0.89,

Table 1. *Continued*

B:

Variable	Validation Cohort			*p*
	$ScvO_2$ < 60 % (*n* = 44)	$ScvO_2$ 60–80 % (*n* = 187)	$ScvO_2$ > 80 % (*n* = 58)	
Age, yr, median (IQR)	62.3 (32.5–81.1)	65.0 (52.8–71.1)	59.5 (50.7–64)	0.04*
Male, *n* (%)	28 (63.6)	118 (63.1)	34 (58.6)	0.81
Comorbidities, *n* (%)				
Cirrhosis	0 (0)	9 (4.8)	5 (8.6)	0.13
Other liver disease	5 (11.4)	27 (14.4)	7 (12.1)	0.81
Chronic renal failure	8 (18.2)	26 (13.9)	6 (10.3)	0.52
Hypertension	10 (22.7)	50 (26.7)	10 (17.2)	0.32
Ischemic heart disease	12 (27.3)	26 (13.9)	4 (6.9)	0.01*
Diabetes	7 (15.9)	33 (17.6)	14 (24.1)	0.4
Chronic obstructive pulmonary disease	7 (15.9)	21 (11.2)	8 (13.8)	0.65
APACHE II score, median (IQR)	20 (17–22)	19 (16–24)	19 (11–25)	0.81
Laboratory variables, median (IQR)				
Baseline lactate (mmol/L)	3.8 (1.8–7.7)	2.8 (1.0–5.9)	2.8 (1.5–4.5)	0.2
Baseline $ScvO_2$ (%)	52 (43–56)	71 (67–76)	84 (82–87)	< 0.001*
Creatinine, µmol/L	118 (97–139)	98.5 (72–182.5)	120 (86–168)	0.8
White blood cell count, × 10^3 µL	13 (10–21.4)	14.3 (7.9–19.3)	16.9 (8.6–25.3)	0.57
Hemoglobin, g/L	106 (89–134)	107 (93.5–126)	111 (99–123)	0.65
Platelet count, × 10^3 µL	152 (108–240)	207 (129–291)	151 (104–256)	0.39
Total bilirubin, µmol/L	25 (11–33)	13 (6–22.5)	14 (6–44)	0.09
Alanine aminotransferease, u//L	43 (26–297)	35 (20–76.5)	28 (20–62)	0.27
Infection sites, *n* (%)				
Lung	11 (25.0)	64 (34.2)	22 (37.9)	0.37
Genitourinary	2 (4.5)	20 (10.7)	8 (13.8)	0.3
Abdominal	6 (13.6)	31 (16.6)	12 (20.7)	0.62
Skin and soft tissue	2 (4.5)	7 (3.7)	2 (3.4)	0.95
Others (central venous system, bone, blood)	5 (11.4)	7 (3.7)	1 (1.7)	0.4

Table 2. Correlation of lactate with $ScvO_2$

$ScvO_2$	Derivation cohort		Validation cohort	
	Correlation with lactate	*p*	Correlation with lactate	*p*
< 60 %	$R^2 = 0.16$	0.01	$R^2 = 0.098$	0.0039
60–80 %	$R^2 < 0.001$	0.83	$R^2 = 0.002$	0.56
≥ 80 %	$R^2 = 0.009$	0.45	$R^2 = 0.005$	0.59

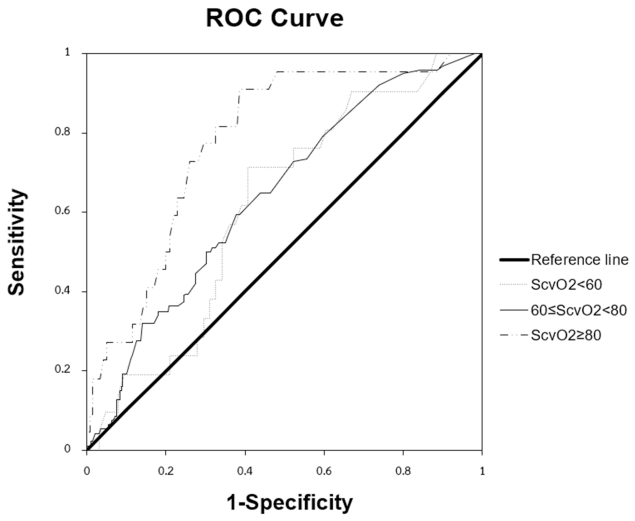

Fig 1. Receiver operating characteristic curve of baseline of serum lactate for predicting 28-day mortality in the Derivation Cohort. The area under the curve (AUC) for the $ScvO_2$ < 60 % group is 0.64, for the 60 %≤$ScvO_2$ < 80 % is 0.65 and for the $ScvO_2$ ≥ 80 % group is 0.94

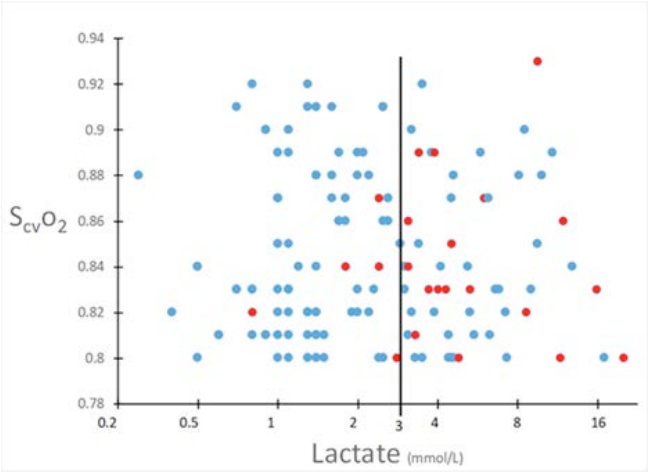

Fig 2. In the $ScvO_2$ ≥ 80 % group, a lactate of 3 mmol/L is the best threshold to predict mortality. Red dots represent non-surviving patients. Blue dots represent surviving patients

p = 0.3) and also not predictive in the 60 % ≤ $ScvO_2$ < 80 % group (AUC = 0.65, 95% CI, 0.56–0.74, p = 0.3). This lack of predictive power was also observed in the Validation Cohort. In contrast, in the $ScvO_2$ ≥ 80 % group from the Derivation Cohort ROC curve analysis showed that the AUC for predicting 28-day mortality was 0.94 (95% CI, 0.88–1.0) (Fig. 1). A lactate level of 3 mmol/L in the group was the optimal threshold in the Derivation Cohort. Using this lactate threshold in the combined Derivation and Validation Cohorts 28-day mortality was 32.7 % when lactate > 3.0 mmol/L while 28-day mortality was 5.6 % when lactate ≤ 3 mmol/L (p = 0.00002) (Fig. 2). Thus, lactate is predictive of 28-day mortality only when $ScvO_2$ ≥ 80 %.

Response to resuscitation

Since lactate arising from global inadequate oxygen delivery is only evident when $ScvO_2$ < 60 % we postulated that lactate clearance in response to resuscitation would be more marked in this group. We further postulated that lactate clearance in response to resuscitation may be less evident at higher $ScvO_2$, which would then suggest that at higher $ScvO_2$, lactate levels may be more heavily influenced by processes other than global tissue hypoxia. To test these hypotheses, we assumed that most resuscitation would have occurred within the first 12 hours after intensive care unit (ICU) admission and we combined Derivation and Validation Cohorts in order to have adequate numbers in subgroups (survivors versus non-survivors in each of three $ScvO_2$ groups). In the $ScvO_2$ < 60 % group lactate clearance was positive (levels decreased from baseline to 12 hours) in survivors but negative in non-survivors. Thus, for $ScvO_2$ < 60 % the difference in lactate clearance between survivors and non-survivors was 3.2 ± 3.0 mmol/L over 12 hours (p < 0.001). In contrast, no significant difference in lactate clearance was found between survivors and non-survivors in the 60 % ≤ $ScvO_2$ < 80 % group (difference between survivors and non-survivors 1.2 ± 2.1 mmol/L over 12 hours, p = 0.75) nor in the $ScvO_2$ ≥ 80 % group (difference between survivors and non-survivors 1.6 ± 2.4 mmol/L over 12 hours, p = 0.14).

Discussion

In our study, we found a correlation between lactate and $ScvO_2$ only when $ScvO_2$ < 60 %. Since both lactate and $ScvO_2$ are (imperfect) markers of tissue hypoperfusion, this correlation is consistent with elevated lactate reflecting tissue hypoperfusion due to inadequate oxygen delivery when $ScvO_2$ < 60 % (Fig. 3 *a*). Resuscitation over the first 12 hours of ICU admission in this $ScvO_2$ group resulted in decreasing lactate in survivors while lactate rose in non-survivors. These results suggest that current guidelines may be appropriate for this $ScvO_2$ group of patients. That is, when $ScvO_2$ < 60 % our results support "guiding resuscitation of sepsis and septic shock to decrease serum lactate in patients with elevated lactate level as a marker of tissue hypoperfusion" [1].

In contrast, absence of a correlation between lactate and $ScvO_2$ when $ScvO_2$ ≥ 60 % suggests that lactate may not be particularly reflective of inadequate whole body oxygen delivery for higher values of $ScvO_2$ (Fig. 3 *b*). Specifically, there is no correlation between lactate and $ScvO_2$ when $ScvO_2$ ≥ 60 % and, furthermore, resuscitation over the first 12 hours of ICU admission does not result in significantly greater lactate clearance in survivors versus non-survivors.

Thus, elevated lactate when $ScvO_2 \geq 60$ % may be heavily influenced by other processes such as accelerated glycolysis driven by sepsis or beta-adrenergic stimulation, reduced entry of pyruvate into the Kreb's cycle, increased conversion of pyruvate to lactate in a reducing environment or decreased lactate clearance. Thus, when $ScvO_2 \geq 60$ %, our results question the current guidelines that resuscitation should be guided by lactate clearance.

Notably, lactate appears to convey very different clinical information when $ScvO_2 \geq 80$ %. When $ScvO_2 \geq 80$ % elevated lactate is predictive of mortality, possibly by discriminating between surviving patients with adequate oxygen delivery versus non-survivors with mitochondrial or other causes of histotoxic hypoxia. This is an important distinction so lactate measurement is helpful. Yet, lactate levels may not be sufficiently reflective of inadequate oxygen delivery (tissue hypoperfusion) in these $ScvO_2 \geq 80$ % patients (Fig. 3 *c*) to provide a firm guide to resuscitation.

Metabolic acidosis is common in patients with sepsis and septic shock and is a prognostic predictor of poor outcome [5]. For example, negative base excess and lactate measurements are associated with adverse clinical outcome [6–7]. However, normal lactate levels are common

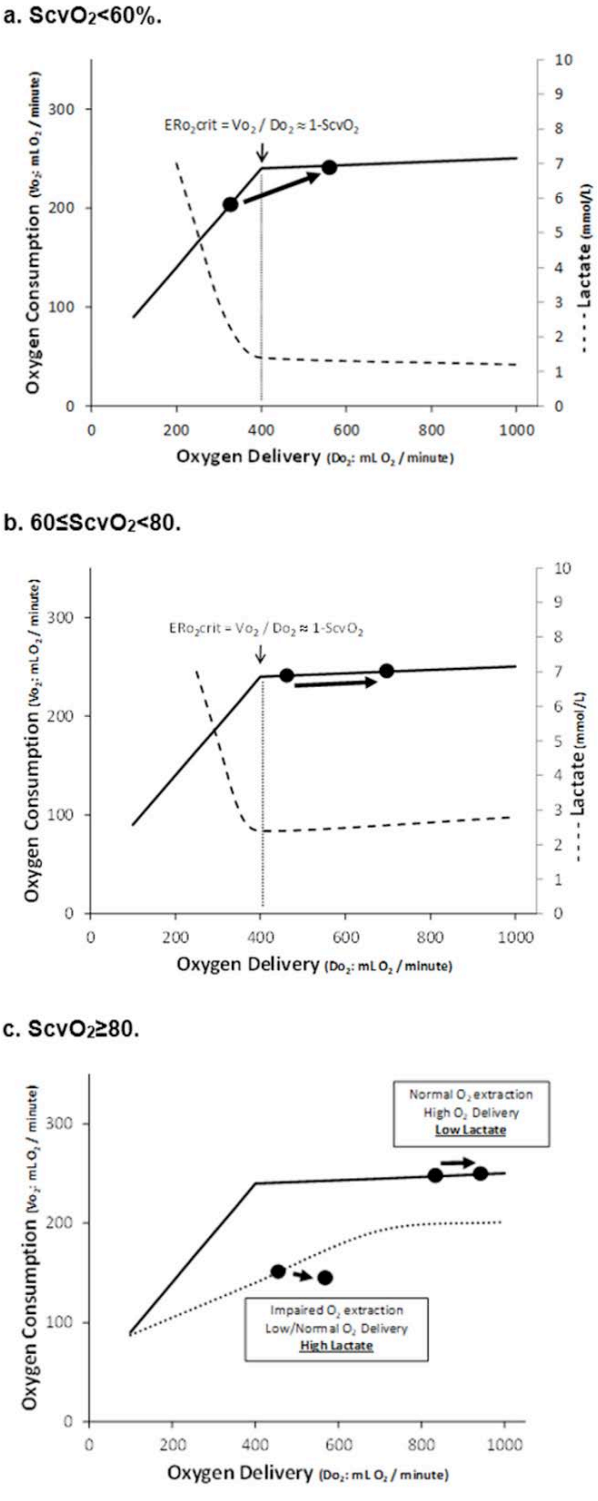

Fig 3. Postulated explanations for observations

A. $ScvO_2 < 60$ %. Some of the patients in this group have approximately normal tissue oxygen extraction capacity and, therefore, normal Vo_2–Do_2 (oxygen consumption — oxygen delivery) relationships (solid line). Pre-resuscitation the problem is that some of these patients have a Vo_2–Do_2 point that falls below the critical oxygen extraction ratio so that oxygen supply limitation exists (anaerobic metabolism = shock) so that $ScvO_2$ (~1 — Vo_2/Do_2) is decreased and lactate (dashed line) is increased. Following resuscitation (bold arrow) aerobic metabolism is restored so that $ScvO_2$ increases and lactate decreases. Thus, lactate correlates with $ScvO_2$ in this group (slope of solid line).

B. $60 \leq ScvO_2 < 80$. These patients have a relatively normal Vo_2–Do_2 relationship (solid line) and a normal-range $ScvO_2$ but lactate (dashed line) is elevated, dominated by causes other than inadequate whole body oxygen delivery (including regional ischemia) so that lactate is not decreased by resuscitation. Resuscitation may drive Do_2 a bit higher but this does not impact tissue oxygenation and lactate may even rise due to factors such as catecholamine-driven increases in glycolysis.

C. $ScvO_2 \geq 80$. This category may be comprised of two types of patients with high $ScvO_2$ for different reasons: 1) those with relatively normal oxygen extraction (Vo_2–Do_2 relationships, solid line) and high oxygen delivery with relatively normal lactate levels and $_2$) those with very impaired oxygen extraction capacity (dotted line) who have high lactate levels. Resuscitation increases an already high oxygen delivery in 1) with little effect on their relatively normal lactate. However, resuscitation in 2) may further impair tissue oxygen extraction capacity, for example, by worsening tissue edema and oxygen diffusion distances. The key differentiating feature between 1) and 2) is lactate. Using survival versus non-survival as a surrogate marker of 1) versus 2), we found a lactate level of 3 mmol/L as the optimal threshold for distinguishing these two groups.

in patients with septic shock and lactate alone is not sufficient to judge success or failure of treatment because it can be affected by many factors. For example, an increase in blood lactate following infusion of adrenaline in septic shock was associated with better survival (31–34). Thus, lactate is an imperfect measure. $ScvO_2$ is also imperfect. Low $ScvO_2$ may be a marker for macrocirculatory failure (inadequate whole body oxygen delivery) and high $ScvO_2$ values may reflect microcirculatory or mitochondrial failure. Both abnormally low and high $ScvO_2$ are associated with increased mortality [36]. Thus, $ScvO_2$ is not, by itself, a good predictor of sepsis mortality [28, 37]. Some studies have demonstrated that venous-to-arterial carbon dioxide difference ($vaCO_2$ gap) might be help to identify patients with persistent global hypoperfusion and guide resuscitation process [42]. A $vaCO_2$ > 6 mmHg reflects a low output state with hypoperfusion and a low $vaCO_2$ of < 6 mmHg reflects impaired utilization of oxygen and low CO_2 production due to mitochondrial dysfunction [43, 44]. Additionally, central venous-to-arterial carbon dioxide difference ($PvaCO_2$ gap) is associated with lactate clearance since $PcvaCO_2$ gap has moderate accuracy for predicting lactate improvement [45]. Therefore, it is likely that adding $vaCO_2$ gap measurements to the lactate / $ScvO_2$ assessment for provide additional information. We did not have $vaCO_2$ gap measurements consistently measured in these cohorts to address this issue here.

Since lactate and $ScvO_2$ both share the underlying determinant of tissue hypoperfusion, we reasoned that the combination of lactate and $ScvO_2$ may be superior to the single measurement of either lactate or $ScvO_2$. We observed that serum lactate and $ScvO_2$ were negatively correlated when $ScvO_2$ < 60 %. There was no correlation between lactate and $ScvO_2$ for patients with mid-range and high $ScvO_2$. This finding is consistent with a previous study, showing that these variables were correlated when oxygen extraction was high (hence low $ScvO_2$) [38]. Correlation suggests that both parameters share an underlying determinant which, from existing knowledge of the determinants of both lactate and $ScvO_2$, implicates tissue hypoperfusion. Patients who responded to initial resuscitation (survived) had a notably greater decrease in lactate in parallel with an increase in $ScvO_2$, further supporting the notion that the combination of high lactate and low $ScvO_2$ reflected tissue hypoperfusion.

Lactate clearance has been shown to be associated with improved survival in critical ill patients [40]. Previous studies demonstrated that a relative lactate clearance of 10 % and early lactate normalization within 6 hours was associated with decreased mortality rate [30, 41]. Consistent with this, our study revealed that in the $ScvO_2$ < 60 % group lactate levels decreased from baseline to 12 hours in survivors but increased in non-survivors. However, lactate clearance was not as useful in distinguishing survivors from non-survivors in the groups with higher $ScvO_2$ and, arguably, maybe not as helpful in guiding resuscitation.

We found that when $ScvO_2 \geq 80$ %, lactate was predictive of 28-day mortality and a lactate level at 3 mmol/L was the optimal discriminatory threshold. However, lactate was not predictive of mortality in the other $ScvO_2$ groups. We postulate that when $ScvO_2 \geq 80$ %, lactate is predictive of mortality, possibly by discriminating between surviving patients with adequate oxygen delivery versus non-survivors with mitochondrial or other causes of histotoxic hypoxia that led to elevated lactate levels (Fig. 3c). That is, $ScvO_2$ > 70 % (and, hence, $ScvO_2 \geq 80$ %) generally reflects adequate oxygen delivery and cellular metabolism. On the other hand, in the case of extreme vasodilatory shock where lactate is rising, high $ScvO_2$ suggests severely impaired tissue oxygen extraction ability due to microcirculatory dysfunction or mitochondrial dysfunction [18]. In this setting lactate discriminates between these two physiologic states; normal lactate when oxygen delivery is adequate but elevated lactate when tissue oxygen extraction capacity is impaired. This is consistent with a previous clinical trial which suggested that high $ScvO_2$ levels were associated with increased mortality because high $ScvO_2$ may reflect impaired extraction of oxygen [27]. Patients with high $ScvO_2$ and high lactate levels had significantly higher rates of mortality [36]. Even with adequate resuscitation of the macro-circulation, tissue hypoxia may persist [39].

Limitations to this study are, first, this a retrospective analysis in two cohorts from different time periods. Second, lactate and $ScvO_2$ were not simultaneously measured in all patients sepsis patients admitted to the ICU so that many screened patients were excluded from analysis. This may result in a risk of selection bias. Third, we were unable to fully evaluate clinical factors and therapeutic interventions including amount of fluid resuscitation and doses of vasopressors that might affect levels of $ScvO_2$ and lactate. Finally, this is a single center study, therefore, our findings may not be generalizable to other settings.

Conclusions

Serum lactate concentration has different characteristics and predictive value at different levels of $ScvO_2$. A high lactate when $ScvO_2$ < 60 % suggests inadequate whole body oxygen delivery (tissue hypoperfusion). However, an elevated lactate does not accurately identify tissue hypoperfusion at higher $ScvO_2$. When $ScvO_2 \geq 80$ % lactate > 3 mmol/L is predictive of mortality. However, an elevated lactate is not a good predictor of mortality for lower values of $ScvO_2$. Serum lactate concentration has different characteristics and predictive value at different levels of central venous oxygen saturation. The combination of lactate and $ScvO_2$ gives insight into the underlying state of shock and potential causes of elevated lactate levels.

Disclosure. The authors declare that they have no competing interests.

Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Authors' ORCID
Sitthikool K. — 0000-0002-9625-4288
Boyd J.H. — 0000-0002-3416-6362
Russell J.A. — 0000-0003-1484-7539
Walley K.R. — 0000-0003-4232-7266

References

[1] *Evans L., Rhodes A., Alhazzani W., et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021; 2: 1–67. DOI: 10.1007/s00134-021-06506-y

[2] *Kraut J.A., Madias N.E.* Lactic acidosis. N Engl J Med. 2014; 371(24): 2309–19. DOI: 10.1056/NEJMra1309483

[3] *Reid M*. Central venous oxygen saturation: analysis, clinical use and effects on mortality. Nurs Crit Care. 2013; 18(5): 245–50. DOI: 10.1111/nicc.12028

[4] *Walton R.A.L., Hansen B.D*. Venous oxygen saturation in critical illness. J Vet Emerg Crit Care (San Antonio). 2018; 28(5): 387–97. DOI: 10.1111/vec.12749

[5] *O'Dell E., Tibby S.M., Durward A., et al*. Hyperchloremia is the dominant cause of metabolic acidosis in the post-resuscitation phase of pediatric meningococcal sepsis. Crit Care Med. 2007; 35: 2390–4. DOI: 10.1097/01.CCM.0000284588.17760.99

[6] *Park M., Azevedo L.C., Maciel A.T., et al*. Evolutive standard base excess and serum lactate level in severe sepsis and septic shock patients resuscitated with early goal-directed therapy: Still outcome markers? Clinics. 2006; 61: 47–52. DOI: 10.1590/s1807-59322006000100009

[7] *Smith I., Kumar P., Molloy S., et al*. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med. 2001; 27: 74–83. DOI: 10.1007/s001340051352

[8] *Vincent J.L., De Backer D*. Circulatory shock. N Engl J Med. 2013; 369: 1726–34. DOI: 10.1056/NEJMra1208943

[9] *Casserly B., Phillips G.S., Schorr C., et al.* Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med. 2015; 43: 567–73. DOI: 10.1097/CCM.0000000000000742

[10] *Zhang Z., Chen K., Ni H., et al*. Predictive value of lactate in unselected critically ill patients: an analysis using fractional polynomials. J Thorac Dis. 2014; 6: 995–1003. DOI: 10.3978/j.issn.2072-1439.2014.07.01

[11] *Ryoo S.M., Ahn R., Shin T.G., et al*. Lactate normalization within 6 hours of bundle therapy and 24 hours of delayed achievement were associated with 28-day mortality in septic shock patients. PLoS One. 2019; 14(6): e0217857. DOI: 10.1371/journal.pone.0217857

[12] *Nichol A.D., Egi M., Pettila V., et al*. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care. 2010; 14: R25. DOI: 10.1186/cc8888

[13] *Levy M.M., Evans L.E., Rhodes A*. The Surviving Sepsis Campaign Bundle: 2018 Update. Crit Care Med. 2018; 46(6): 997–1000. DOI: 10.1097/CCM.0000000000003119

[14] *Jansen T.C., Bommel J.V., Schoonderbeek F.J., et al*. LACTATE study group. Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010; 182: 752–61. DOI: 10.1164/rccm.200912-1918OC

[15] *Jones A.E., Shapiro N.I., Trzeciak S., et al*. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. JAMA. 2010; 303: 739–46. DOI: 10.1001/jama.2010.158

[16] *Rivers E.P., Ander D.S., Powell D*. Central venous oxygen saturation monitoring in the critically ill patient. Curr Opin Crit Care. 2001; 7: 204–11. DOI: 10.1097/00075198-200106000-00011

[17] *Muckart D.J, Bhagwanjee S*. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. Crit Care Med. 1997; 25(11): 1789–95. DOI: 10.1097/00003246-199711000-00014

[18] *Walley K.R.* Use of Central Venous Oxygen Saturation to Guide Therapy. Am J Respir Crit Care Med. 2011; 184(5): 514–20. DOI: 10.1164/rccm.201010-1584CI

[19] *Bellomo R., Reade M.C., Warrillow S.J.* The pursuit of a high central venous oxygen saturation in sepsis: growing concerns. Crit Care. 2008; 12(2): 130. DOI: 10.1186/cc6841

[20] *Rivers E., Nguyen B., Havstad S., et al*. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345(19): 1368–77. DOI: 10.1056/NEJMoa010307

[21] *Jones A.E., Shapiro N.I., Trzeciak S., et al*. Emergency Medicine Shock Research Network I: lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010; 303: 739–46. DOI: 10.1001/jama.2010.158

[22] *Peake S.L., Delaney A., Bailey M., et al.* Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014; 371: 1496–506. DOI: 10.1056/NEJMoa1404380

[23] *Mouncey P.R., Osborn T.M., Power G.S., et al.* Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015; 372: 1301–11. DOI: 10.1056/NEJMoa1500896

[24] *Yealy D.M., Kellum J.A., Huang D.T., et al*. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014; 370: 1683–93. DOI: 10.1056/NEJMoa1401602

[25] *Singer M., Deutschman C.S., Seymour C.W., et al*. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 23; 315(8): 801–10. DOI: 10.1001/jama.2016.0287

[26] *Bracht H., Hänggi M., Jeker B., et al*. Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: an observational study. Critical Care. 2007; 11: R2. DOI: 10.1186/cc5144

[27] *Textoris J., Fouché L., Wiramus S., et al.* High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care. 2011; 26; 15(4): R176. DOI: 10.1186/cc10325

[28] *Lee Y.K., Hwang S.Y., Shin T.G., et al*. Prognostic value of lactate and central venous oxygen saturation after early resuscitation in sepsis patients. PLoS One. 2016; 11(4): e0153305. DOI: 10.1371/journal.pone.0153305

[29] *Casserly B., Phillips G.S., Schorr C., et al*. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care. 2015; 43: 567–573. DOI: 10.1097/CCM.0000000000000742

[30] *Puskarich M.A., Trzeciak S., Shapiro N.I., et al*. Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest. 2013; 143: 1548–1553. DOI: 10.1378/chest.12-0878

[31] *Suetrong B., Walley K.R*. Lactic Acidosis in Sepsis: It's not all anaerobic implications for diagnosis and management. CHEST. 2016; 149(1): 252–261. DOI: 10.1378/chest.15-1703

[32] *Rivers E.P., Elkin R., Cannon C.M*. Counterpoint: should lactate clearance be substituted for central venous oxygen saturation as goals of early severe sepsis and septic shock therapy? No. Chest. 2011; 140: 1408–1413. DOI: 10.1378/chest.11-2563

[33] *Hernandez G., Castro R., Romero C., et al*. Persistent sepsis-induced hypotension without hyperlactatemia: is it really septic shock? J Crit Care. 2011; 26: e439– e414. DOI: 10.1016/j.jcrc.2010.09.007

[34] *Omar S., Burchard A.T., Lundgren A.C., et al*. The relationship between blood lactate and survival following the use of adrenaline in the treatment of septic shock. Anaesth Intensive Care. 2011; 39(3): 449–455. DOI: 10.1177/0310057X1103900316

[35] *Rowan K.M., Angus D.C., Bailey M., et al.* Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis. N Engl J Med. 2017; 376(23): 2223–2234. DOI: 10.1056/NEJMoa1701380

[36] *Pope J.V., Jones A.E., Gaieski D.F., et al.* Multicenter study of central venous oxygen saturation ($ScvO_2$) as a predictor of mortality in patients with sepsis. Ann Emerg Med. 2010; 55(1): 40–46.e1. DOI: 10.1016/j.annemergmed.2009.08.014

[37] *Shin T.G., Jo I.J., Hwang S.Y., et al.* Comprehensive interpretation of central venous oxygen saturation and blood lactate levels during resuscitation of patients with severe sepsis and septic shock in the emergency department. SHOCK. 2016; 45(1): 4–9. DOI: 10.1097/SHK.0000000000000466

[38] *Bisarya R., Shaath D., Pirzad A., et al*. Serum lactate poorly predicts central venous oxygen saturation in critically ill patients: a retrospective cohort study. J Intensive Care. 2019; 7:47. DOI: 10.1186/s40560-019-0401-5

[39] *Roberts J.K., Disselkamp M., Yataco A.C*. Oxygen Delivery in Septic Shock. Ann Am Thorac Soc. 2015; 12(6): 952–955. DOI: 10.1513/AnnalsATS.201501-069CC

[40] *Joshi R., de Witt B., Mosier J.M*. Optimizing oxygen delivery in the critically ill: the utility of lactate and central venous oxygen saturation ($ScvO_2$) as a roadmap of resuscitation in shock. The Journal of emergency medicine. 2014; 47(4): 493–500. DOI: 10.1016/j.jemermed.2014.06.016

[41] *Nguyen H.B., Rivers E.P., Knoblich B.P., et al*. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004; 32 (8): 1637–42. DOI: 10.1097/01.ccm.0000132904.35713.a7

[42] *Vallet B., Pinsky M.R., Cecconi M*. Resuscitation of patients with septic shock: please 'mind the gap'! Intensive Care Med. 2013; 39: 1653–5. DOI: 10.1007/s00134-013-2998-5

[43] *Vallée F., Vallet B., Mathe O., et al*. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med. 2008; 34: 2218–25. DOI: 10.1007/s00134-008-1199-0

[44] *Ospina-Tascon G.A., Bautista-Rincon D.F., Umaña M., et al*. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Crit Care. 2013; 17: R294. DOI: 10.1186/cc13160

[45] Mesquida J., Gruartmoner G., Espinal C., et al. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock Crit Care. 2015; 19(1): 126. DOI: 10.1186/s13054-015-0858-0