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The role of central venous oxygen saturation, blood lactate, and central venous-to-arterial carbon dioxide partial pressure difference as a goal and prognosis of sepsis treatment

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ABSTRACT

Objective: The current practice in treatment of severe sepsis and septic shock is to ensure adequate oxygenation and perfusion in patients, along with prompt administration of antibiotics, within 6 hours from diagnosis, which is considered the "golden hour" for the patients. One of the goals of treatment is to restore normal tissue perfusion. With this goal in mind, some parameters have been used to determine the success of treatment and mortality rate; however, none has been proven to be the best predictor of mortality rate in sepsis patients. Despite growing evidence regarding the prognostic indicators for mortality in sepsis patients, inconsistent reports exist.
Study selection: This review comprehensively summarizes the reports regarding the frequently used parameters in sepsis including central venous oxygen saturation, blood lactate, and central venous-to-arterial carbon dioxide partial pressure difference, as prognostic indicators for clinical outcomes in sepsis patients. Moreover, consistent findings and inconsistent reports for their pathophysiology and the potential mechanisms for their use as well as their limitations in sepsis patients are presented and discussed. Finally, a schematic strategy for potential management and benefits in sepsis patients is proposed based upon these current available data.
Conclusion: There is currently no ideal biomarker that can indicate prognosis, predict progression of the disease, and guide treatment in sepsis. Further studies are needed to be carried out to identify the ideal biomarker that has all the desired properties.

1. Introduction

Sepsis is currently an extensive worldwide problem. It is the fourth leading cause of death, with the mortality rate reaching 70% [1]. Since the publication of the "Early goal directed therapy" protocol by Rivers et al [2] in 2001, the setting up of "goals" and the use of central venous oxygen saturation ($ScvO_2$) as one of the markers for adequate tissue perfusion has proven to be the beginning of a new era of sepsis management [3,4]. These goals aimed to restore tissue perfusion at the cellular level, which is when it exceeds the blood pressure or perfusion information achieved by solely physical examination, central venous pressure, or even urine output [5,6] and also using the $ScvO_2$ as the final goal which has proved to be a good parameter to use in cases of sepsis [7,8]. It has been over a decade since the first release of that report, and new parameters or new "goals" have been proposed to enhance the use of the protocol. Despite this improvement, an optimal parameter to best predict the mortality rate in sepsis patients is still to be found. Moreover, inconsistent reports also exist regarding the reliability of some parameters.

This review aims to be a comprehensive summary of the most often used parameters as well as describing novel potential parameters to be used in sepsis, including $ScvO_2$, lactate, and central venous-to-arterial carbon dioxide partial pressure difference (ΔPCO_2). The consistent as well as the contradictory reports regarding the use of these parameters as prognostic indicators in sepsis are presented and discussed. The information obtained from these reports should provide a great deal of insight in helping to redefine the therapeutic management protocol to improve the care of sepsis patients in the near future.

1.1. Central venous oxygen saturation and mortality in sepsis

Central venous oxygen saturation is a level of oxygen saturation measured from the superior vena cava. Its value is the balance between

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oxygen delivery and oxygen consumption (VO_2), indicating how much oxygen remains after delivery to the cells. The physiological value is greater than 70% [9]. This is also the last goal to be achieved according to the early goal-directed therapy [2]. Central venous oxygen saturation is used to indicate an adequate level of oxygenation at the cellular level. In a standard protocol, if the level of $ScvO_2$ is less than 70%, attempts to increase oxygen content will be performed by adequate oxygenation; transfusion of packed red blood cells to increase hemoglobin level to 10%; increased cardiac contractility by using inotropic drugs; and avoidance of unnecessary use of oxygen by the cells by reducing fever, shivering, pain, or work of breathing. These procedures are carried out along with an intermittent monitoring of $ScvO_2$[10]. Because $ScvO_2$ changes rapidly, frequent measurement of $ScvO_2$ must be used after an intervention is implemented. However, no difference in mortality was found between intermittent and continuous $ScvO_2$ monitoring [11].

Central venous oxygen saturation monitoring during resuscitation of patients with sepsis has been shown to be a crucial step. In pediatric patients, it has been shown that patients with intermittent $ScvO_2$ monitoring had a lower 28-day mortality rate compared to the group without $ScvO_2$ monitoring [7,12]. It has also been demonstrated that early low initial $ScvO_2$ (<70%) was associated with increased mortality in both pediatric and adult patients [8]. All of these findings indicated that $ScvO_2$ could play an important role in the guidance for resuscitation and prognosis prediction.

Despite those reports, recent studies have demonstrated that an extremely high $ScvO_2$ was associated with an increased mortality in sepsis patients [8,13,14]. The mean of the maximal $ScvO_2$ value was found to be lower in the survival group, whereas the mortality rate was higher in the group with a maximal $ScvO_2$ higher than 80% [14]. Consistent with this report, another study demonstrated that patients with a normal value of maximal $ScvO_2$ value (70%-89%) during the first 6 hours of initial resuscitation had the lowest mortality, whereas patients with a higher value of maximal $ScvO_2$ (≥90%) had a higher mortality rate, and those with a lower value of maximal $ScvO_2$ (<70%) had the highest mortality rate [13,14]. This is due to the fact that the mean $ScvO_2$ at the initial phase of septic shock was measured to be 73% [13], whereas the initial SvO_2 due to microcirculatory dysfunction was 68.8% [15], roughly close to the goal of 70% set up in the guideline. Moreover, this proposed concept of $ScvO_2$ level has been challenged because many recent studies demonstrated the disadvantages of $ScvO_2$ greater than 70% for the prediction of a positive prognosis for septic patients. This is due to the fact that even with the achieved $ScvO_2$ goal at 70% after resuscitation, it might not reflect adequate tissue oxygenation because the cells may not be able to use oxygen and thus never reflect the real end point of resuscitation [14,16]. The most plausible reason for this phenomenon is due to an impairment of the microcirculation or mitochondrial dysfunction. Moreover, this condition can lead to cell apoptosis if it is caused by mitochondrial dysfunction [17]. As a result, $ScvO_2$ may predict the best outcome when its levels are within 70% to 80% after resuscitation.

In addition, $ScvO_2$ has been used to replace the mixed venous oxygen saturation ($SmvO_2$), which was the previous standard protocol. This was due to the fact that $SmvO_2$ has to be collected from the pulmonary artery which is more difficult to access than the superior vena cava. However, recent study demonstrated that $ScvO_2$ had no correlation to $SmvO_2$ in sepsis. The reason behind this might be due to sepsis-related vasodilation in the digestive tract and diminished oxygen consumption, leading to a faulty elevated $SmvO_2$[18]. The use of $ScvO_2$ or $SmvO_2$ has been much debated with the final decision being that the latter is a more reliable parameter [18,19]. Nevertheless, $ScvO_2$ is still currently used as an acceptable parameter for a goal of resuscitation in both adults and children with sepsis [20,21]. A comprehensive summary of the reports regarding the roles of $ScvO_2$ as a prognostic indicator in sepsis is shown in Table 1.

1.2. Lactate and mortality in sepsis

Perfusion to organs in the late septic phase is usually decreased, causing a reduction in cytochrome C oxidase activity in the mitochondrial electron transport chain due to inadequate oxygen delivery to mitochondria [22]. This leads to decreased ATP production, causing the cells to increase levels of anaerobic metabolism. Lactate production is a product of anaerobic respiration under these conditions of poor perfusion [23,24]. In a healthy body, elimination of lactate occurs via 2 different processes. Seventy percent of lactate will be used as a substrate for gluconeogenesis, being converted to pyruvate and eventually glucose in the liver. The remaining lactate will be changed into pyruvate in mitochondria-rich tissues such as skeletal myocytes, cardiac myocytes, and proximal tubule cells, to be further used in glycolysis [25]. Under normal physiological conditions, the lactate half-life is approximately 20 minutes [26], so a persistently high level of lactate reflects its continuous production or lack of elimination. Previous studies demonstrated that sepsis patients with a lactate level of greater than 4 mmol/L had a poor prognostic outcome independent of hypotension [27].

Lactate clearance is defined as the decrease of lactate after the treatment compared to initial lactate level [28]. It usually occurs after successful resuscitation which indicates adequate tissue perfusion. According to this concept, lactate clearance has been proposed as alternative "goal" of resuscitation in patients with sepsis. It has been shown that using greater than 10% lactate clearance from the initial lactate level within 6 hours after resuscitation as a goal can increase survival rate [29,30]. A following randomized control trial showed noninferiority of lactate clearance when compared to $ScvO_2$ in inhospital mortality [28]. Moreover, there is a correlation between a greater lactate clearance with a better survival rate, with a normalizing of lactate to the level of less than 2 mmol/L being shown to lead to the greatest survival rate [31,32]. The latest Sepsis Bundle Care recommends the use of a cutoff point of a lactate level of greater than 4 mmol/L to indicate severe sepsis, whereas the normalization of lactate indicates the end point of resuscitation with respect to normalized lactate [20].

Despite these reports, lactate usage is still limited as a prognostic indicator in sepsis patients. This is due to the fact that lactate can be elevated from other causes other than hypoperfusion. These causes can be from increase production or decrease elimination of lactate, such as an increase rate of glycolysis, increase substrate entry into glycolysis, or hepatic disease [33]. False elevation of lactate could be due to external sources of lactate such as lactated Ringer's solution and blood components which contained red blood cells [16], and blood preservation techniques before the measurement of plasma lactate levels can also alter lactate level results. To reduce this false elevation reading of lactate, it has been recommended to measure the lactate level from the blood sample within 15 minutes or use a point-of-care device, and blood should be kept on ice if a longer time is needed before the test [34]. Fortunately, it has been shown that use of a tourniquet has no effect on the change in the blood lactate level [35]. Although arterial lactate has been used as standard for lactate measurement, it is an invasive and time-consuming method compared to the venous lactate determination. Recent evidence had confirmed that venous lactate determination can replaced the arterial lactate determination method because studies confirm that levels of venous lactate are closely correlated to arterial lactate [36,37]. Currently, there is no proven effective method to directly decrease the amount of lactate in the blood, and no data suggest the frequency of the lactate determination in the blood in this group of patients. A comprehensive summary of the reports regarding the roles of lactate as a prognostic indicator in sepsis is shown in Table 2.

1.3. Central venous-to-arterial carbon dioxide partial pressure difference and mortality in sepsis

Central venous-to-arterial carbon dioxide partial pressure difference (pCO_2 gap; $P(cv\text{-}a)CO_2$) is the difference between carbon dioxide (CO_2)