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Research review

New directions for sepsis and septic shock research

Nivin Sharawy, MD,[*,1] *and Christian Lehmann, MD, PhD, FRCPC*[1]

Department of Anesthesia, Dalhousie University, Halifax, Nova Scotia, Canada

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ABSTRACT

Background: Septic shock is a frequent complication in intensive care unit that can result in multiple organ failure and death. In addition, recent data suggested that severe sepsis and septic shock represent an economic burden. Therefore, septic shock is an important public health problem.

Method: In this review, we will focus on the recent evidences concerning the stages of septic shock, the complex macrocirculation and microcirculation relationship, and the importance of those evidences for future resuscitation goals and therapeutic strategies during late septic shock.

Result: Recently, two stages of septic shock are suggested. In early stage, hypovolemia is the main contributing factor. During this stage, macrocirculatory and microcirculatory changes run parallel, and fluid resuscitation seems to be effective in restoring the hemodynamic parameters. Late stage of septic shock is characterized by complex microcirculation and macrocirculation relationship.

Conclusions: Although early goal-directed therapy is a stepwise approach in the treatment of septic shock, tissue perfusion remains an important factor that contributes to septic shock outcome. Because appropriate monitoring of tissue perfusion is a matter of debt, the ideal therapeutic strategy remains a controversial issue that needs further investigations.

1. Introduction

Septic shock is the primary cause of death in critical care units because of tissue hypoperfusion and multiorgan failure. Infection and mediators induced by infection result in hypovolemia, vascular failure, and heart failure [1,2].

Four physiologic subtypes of shock are known as follows: hypovolemic, cardiogenic, distributive, and obstructive shock. Septic shock was recently classified, according to pathophysiological background, into two stages as follows: the early hypovolemic and the late vascular and myocardial circulatory dysfunction stage [3].

Although warm shock, mediated by endotoxin-induced abnormal vasodilation, is a major characterization for distributive type septic shock, cold cardiogenic shock during sepsis, resulting from cardiac poor perfusion during septic shock or underlying cause of sepsis, is associated with elevated troponin and B-type natriuretic peptide levels (cardiac dysfunction markers) and diminished cardiac function diagnosed by echocardiography [4]. During hypovolemic shock (the

* *Corresponding author*. Department of Anesthesia, Dalhousie University, Sir Charles Tupper Medical building, Room 6H-1, 5850 College street, Halifax, Nova Scotia, Canada B3H 2Y9. Tel.: +1 902 401 2942; fax: +1(902) 423-9454.
E-mail address: nivinsharawi@gmail.com (N. Sharawy).

[1] Both N.S. and C.L. equally contributed to review.

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primary deranged is venous return) and cardiogenic shock (the primary deranged is the pump), organs are affected through hypoperfusion-induced hypoxia. Meanwhile, the distributive shock is characterized by the direct toxic effect and higher oxygen demand of organs. At the end stage, the irreversible shock exhibits universal hypodynamic features of unresponsiveness to catecholamines, reduced metabolism, hypothermia, and reduced oxygen consumption regardless of the etiology of shock. At this point, the arterioles–capillaries system or/and the cellular mitochondria stop functioning [5].

For several decades, the regulation of arterial blood pressure has been considered as an important target in the treatment of septic shock. However, restoration of mean arterial blood pressure (MAP), especially in the late stage of circulatory failure, does not always equate to blood flow [1]. In addition, increasing blood pressure to certain end points using different vasopressors failed to improve tissue perfusion, oxygenation, and to reduce the mortality rate [6,7].

Because resuscitation strategy directed at restoring systemic oxygen delivery and improving tissue oxygenation has been suggested to improve survival rate significantly, therapy should be guided by adequate tissue perfusion parameters [1,8]. A recent International Sepsis Definitions Conference [9] recommended expanding the diagnostic criteria for sepsis to include changes in the mental status, organ dysfunction parameters, acute oliguria, hyperlactatemia (>3 mmol/L), and decreased capillary refill or mottling (global and regional hypoperfusion criteria).

Recently, it became important that tissue hypoperfusion be recognized, and that therapeutic strategies should trigger not only normal blood pressure but also normal tissue perfusion, especially in the late stage of circulatory failure.

This narrative review aims are (1) to clarify endothelium dysfunction and endothelium heterogeneity as pathophysiological background for the vascular failure and the complex relation between conductive and resistance blood vessel during the late stage of septic shock, (2) to discuss different methods of tissue perfusion assessment, and (3) to provide an overview of the available clinical data on the current vasopressor agents and their effectiveness in restoring the tissue perfusion [7]. The future approach is to improve the tissue perfusion, through novel alternative therapies.

2. Discussion

2.1. *Endothelium dysfunction and heterogeneity*

Vasopressor–refractory hypotension (vasoplegia, vascular failure) is contributed to many factors including endothelium dysfunction, a decrease in vasoconstrictor tone, and vasopressin deficiency. Although therapeutic interventions target these mechanism successes to restore the blood pressure, they fail to improve tissue perfusion [2].

The initial excitement of nitric oxide (NO) has been transformed into many new explorations, including NO as an endothelium-derived relaxing factor of vascular smooth muscle and vasodilator mediator during sepsis. However, more than one endothelium-derived relaxing factor are found recently to be produced by endothelium and cause vasodilatation. Recently, it was observed that NO-mediated endothelium vasorelaxation occurs in large conductive arteries, whereas the endothelium-dependent relaxation of peripheral resistance arteries does not depend mainly on NO production. The mystery surrounding the role of other endothelium-derived hyperpolarizing factors during septic shock has not been solved, and the roles of NO and superoxide interactions with the biological effects attribute mainly to peroxynitrite rather than NO in septic-induced vasoplegia have been questioned in recent years [10,11].

One of the key features of sepsis is the production of reactive oxygen species (ROS) (e.g., superoxide), which is synthesized in endothelial cells by the mitochondrial electron transport chain, xanthine oxidase, uncoupled nitric oxide synthases and nicotinamide adenine dinucleotide phosphate-oxidases. Superoxide rapidly interacts with NO, which results in formation of peroxynitrite [12]. Some studies reported that peroxynitrite could be responsible for many of the vascular alterations associated with shock (endothelial dysfunction and vascular hyporeactivity) [13–15]. In addition, septic-induced NO upregulation may be adaptive and preserves the microcirculatory patency and function through neutralization of the oxygen-derived species, modulation of blood coagulation, and improving the mitochondrial respiration in tissues [16]. Selective inhibition of peroxynitrite formation could represent a preferred approach over pharmacologic inhibition of NO generation during septic shock [16] Figure.

2.2. *Tissue perfusion monitoring: downside currently used biomarkers and microcirculation*

The high mortality rate during the late stage of septic shock, in spite of the early goal-directed therapy that based on optimization of MAP, central venous pressure, urine output, and central venous oxygen saturation ($ScvO_2$), raised the need for the new determinant prognostic factors for guiding therapy after the initial resuscitation [17,18].

Several tissue perfusion parameters have been explored. Among them are hemodynamic parameters, lactate, mixed (SvO_2), or central venous oxygen saturations ($ScvO_2$), peripheral perfusion (capillary refill time and central-to-toe temperature difference), venous-arterial pCO_2 gradient (P(cv-a) CO_2), gastric tonometry, and more recently, sublingual microcirculatory flow [19–24]. Different clinical studies have reported the limitation of currently used perfusion parameters, and that general parameters such as lactate and venous oxygen saturation (SvO_2, $ScvO_2$) could occasionally be misleading or noninterpretable [21,23–26]. In addition, because of the extreme complexity of sepsis-induced circulatory failure, none of the markers have earned universal acceptance as the unique parameter to guide late-stage septic shock resuscitation [3,21].

In this section, we will briefly review basic foundations and limitations of different global and regional perfusion parameters currently used during septic shock.

2.3. *Lactate*

The strong prognostic importance of hyperlactatemia and its correlation with other hemodynamic and perfusion