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Influence of obesity on sepsis

Vidula Vachharajani *

Department of Anesthesiology, Medical Center Blvd, Wake Forest University School of Medicine, Winston-Salem, NC 27157, United States

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Abstract

Sepsis is the leading cause of death in non-coronary intensive care units worldwide, with a very high cost of care. There is a growing body of evidence suggesting that the increase in morbidity associated with severe obesity in critically ill patients results in increased resource utilization adding further to the cost of care. There is a relative paucity of information regarding the pathophysiology and treatment of obese critically ill patients, especially with sepsis. Obesity as an exclusion criterion in landmark trials is partly responsible for this paucity. While the preventive strategies for obesity will be the most definitive long-term solution, it will take a long time to affect outcomes in our intensive care units. In the meantime, our hospitals, including the intensive care units must continue to treat obese/morbidly obese critically ill patients with sepsis, making it essential to study and understand the pathophysiology and develop treatment strategies for obese with sepsis. Available laboratory data suggests an increased inflammatory response in obese septic individuals. However, the association between obesity and sepsis in the clinical setting is unclear due to controversial results. This article reviews the available clinical and laboratory data that addresses the effects of obesity on sepsis.

Keywords: Obesity; Sepsis; Critical care; Leukocyte adhesion

1. Sepsis and septic shock

Sepsis has been known to mankind for 2700 years [1]. The modern day definition of sepsis was derived from the consensus conference between the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) in 1992 [2] as described in Table 1. Sepsis is defined as a systemic inflammatory response to infection, which, when associated with one or more organ systems, is considered as severe failure. When sepsis is associated with shock, which is refractory to fluid resuscitation, the patient is considered to be in septic shock. Sepsis and septic shock are the leading causes of death in the non-coronary artery disease intensive care units worldwide with substantial cost of care [3]. Not only has the rate of hospitalization due to sepsis doubled over the last decade and has exceeded the expected rate of hospitalization, but the overall mortality has also increased considerably during that period [4]. This clearly underscores the fact that morbidity and mortality associated with sepsis causes an economic burden on the society.

1.1. Pathophysiology of sepsis and septic shock

The pathophysiology of sepsis consists of a well-orchestrated host response to invading organisms. This response, which is a local process initially, becomes an overwhelming systemic response in cases of severe sepsis and septic shock. The inability of the host to recognize self from non-self can be viewed as a critical central theme to this exaggerated response.

Host response is implicated in the excessive morbidity and mortality associated with sepsis due to the collateral damage that it causes in the form of multiple organ failure. There are several findings that support the view that host response is the most critical determinant of outcome in sepsis. (1) Mortality is comparable in culture negative and culture positive patients with sepsis [5]. (2) Mortality with sepsis and septic shock is directly proportional to the number of organ systems involved in the multiple organ failure [6]. (3) There is a direct correlation between the number

* Tel.: +1 336 716 4498; fax: +1 336 716 8190.
E-mail address: vvachhar@wfubmc.edu.

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Table 1
Key definitions in sepsis and septic shock

Infection	Phenomenon characterized by inflammatory response to the presence of microorganism or invasion of normally sterile host tissue by those organisms
Bacteremia	Presence of viable bacteria in the blood
Systemic inflammatory response syndrome (SIRS)	Presence of two or more of the following: (1) temperature >38 or <36 °C; (2) heart rate >90/min; (3) respiratory rate >20 or PaCO2 <32 mmHg; (4) white blood cell count >12,000 or <4000/cu mm or presence of bands >10%
Sepsis	SIRS in the presence of infection
Severe sepsis	Sepsis associated with organ dysfunction
Septic shock	Sepsis induced hypotension despite adequate fluid resuscitation
Sepsis induced hypotension	Systolic blood pressure <90 mmHg or decrease of >40 mmHg from the baseline in the absence of other causes of hypotension
Multiple organ dysfunction syndrome (MODS)	Presence of altered organ function in acutely ill patient such that homeostasis cannot be maintained without intervention

From consensus conference between ACCP and SCCM[2].

of Systemic Inflammatory Response Syndrome (SIRS) criteria and mortality in critically ill patients [7]. These host responses are described in the following sections.

2. Cellular response

Tissue macrophages, monocytes, other myeloid cells, and to some extent, endothelial cells contribute to the cellular response seen in sepsis [8]. Following an inflammatory stimulus, these cells respond as a first line of defense. These cells recognize pathogens via pattern recognition receptors that have an ability to interact with microbial structures [9]. The interactions that follow between these pathogens and the host cells incite a variety of changes, leading up to activation of inflammatory and coagulation cascades [8,10]. This activation further leads to the release of soluble mediators that affect the endothelium and further activate inflammatory cells, making this process self-perpetuating.

3. Activation of inflammatory and coagulation pathways

3.1. Inflammatory cascade

It is widely accepted that the invasion of pathogen is recognized due to the surface features of the microbial pathogen via pattern recognition receptors [11,12] that results in the generation of a network of host response signals that alert the host of the potential threat [10,13]. The pathogens lead to activation of the complement cascade [14], cytokines [15], and release inflammatory mediators from a variety of cell types such as monocytes and endothelial cells, in addition to activation of the coagulation cascade [8]. These changes manifest clinically as SIRS. To dampen the pro-inflammatory response in sepsis, an anti-inflammatory response is activated. This is termed as compensatory anti-inflammatory response syndrome (CARS). It is the balance between SIRS and CARS that determines the fate of the surrounding tissue. Under ideal circumstances, these two phases are coordinated and well balanced. Uncoupling of the two phases or an excessive inflammatory response is the mechanism by which tissue damage occurs [16].

3.2. Coagulation cascade

During sepsis, the circulating cells and macrophages express tissue factor on their surface. Tissue factor (TF) is responsible for the initiation of the extrinsic pathway for coagulation in sepsis, but it is through the cross talk and feedback between the intrinsic and extrinsic pathways of coagulation that this process is amplified. The coagulation cascade is comprised of a series of reactions that once activated the immediate downstream substrate via serine proteases. The extrinsic coagulation pathway is considered to be the initiator and intrinsic pathway to be the amplifier of this process as depicted in Fig. 1. These pathways generate thrombin and fibrin. Fibrin stabilizes the platelet plug and immobilizes the pathogen on the surface of leukocyte ready to be engulfed and disposed.

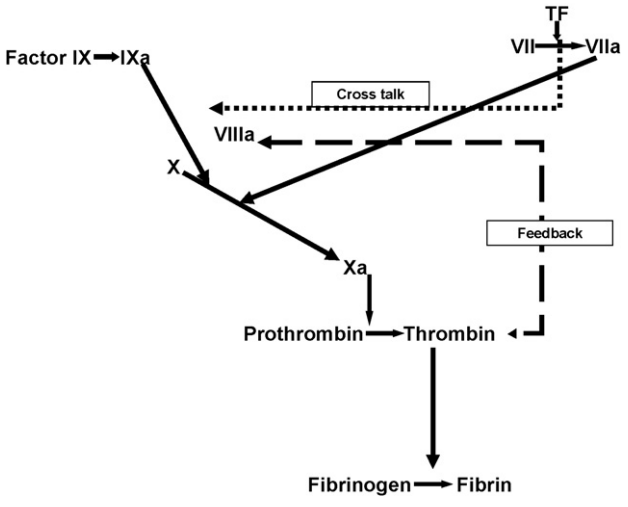

Fig. 1. Coagulation cascade in sepsis. Intrinsic pathway is considered as an initiator and extrinsic pathway as an amplifier of this process through cross talk and feedback mechanisms.