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UNDERSTANDING THE DISEASE

Understanding circulatory failure in sepsis

Andreas Bloch, David Berger and Jukka Takala*

Introduction

Septic shock or acute circulatory failure in sepsis causes a mismatch between tissue perfusion and metabolic demands. The heart, the vasculature and alterations in various tissue and cellular functions are involved in the pathophysiology. The clinical presentation can be highly variable, changes over time and is modified by preceding and concomitant treatment and comorbidities. The clinical hallmarks of septic shock are signs of tissue hypoperfusion, hypotension or need for vasopressors to prevent hypotension, despite adequate fluid resuscitation. Signs of tissue hypoperfusion vary and can include impaired capillary perfusion, oliguria, elevated blood lactate and altered mentation. The blood pressure level that is clinically relevant varies between patients, and "adequate" fluid resuscitation is highly subjective. Therefore, septic shock defies explicit, objective definitions, as shown by the current debate around attempts to define it [1, 2]. Nevertheless, increasing severity of circulatory failure is associated with increasing mortality [3]. Delayed treatment increases the severity of circulatory failure in sepsis, necessitates more support with fluids and vasoactive drugs, and increases mortality [4].

Volume, circuit factors and venous return

The blood volume consists of unstressed volume and stressed volume. The unstressed volume fills the vasculature before any vessel wall tension develops. The volume that causes wall tension is the stressed volume. Any change in vascular tone shifts volume between the stressed and unstressed volume. The stressed volume and vascular compliance define the mean systemic filling pressure (MSFP). The difference between the MSFP and the right atrial pressure is the driving pressure for venous return. In the steady state, venous return must equal cardiac output [5]. Accordingly, venous return influences cardiac output and vice versa. Sepsis decreases the stressed volume via two mechanisms: by loss of total volume due to increased vascular permeability and by shift from stressed to unstressed volume due to vasodilatation. Both mechanisms reduce the driving pressure for venous return and consequently cardiac output (Fig. 1a). The relative contribution of these mechanisms is highly variable. If volume loss due to increased permeability predominates, fluids are needed to restore both unstressed and stressed volume. In contrast, if vasodilation is the main mechanism, vasopressors should be combined with judicious use of fluids. The hypotensive patient with cold periphery is more likely to have an absolute volume deficit, whereas one with preserved peripheral perfusion is likely to benefit from vasoconstriction. In both scenarios, treatment should normalize venous filling and capillary perfusion. Rapid increase in venous filling in response to fluids suggests cardiac dysfunction.

Changes in myocardial function

Profound but reversible myocardial depression in septic shock was first described in 1984 [6]. Administration of endotoxin to normal humans also resulted in impaired left ventricular (LV) function independent of changes in vascular resistance and ventricular volume [7]. Despite decades of research, the relevance of myocardial function changes in sepsis remains unclear. Reduced LV systolic function is common in septic shock patients without previous cardiac disease and the occurrence rate increases over time—ranging from ca. 40 % on day 1 up to ca. 60 % on day 3 [8]. A concomitant increase in end-diastolic volume may help to defend cardiac output and possibly improve prognosis [8, 9]. Diastolic dysfunction—present in up to half of the patients—is a major predictor of mortality in septic shock

*Correspondence: jukka.takala@insel.ch
Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

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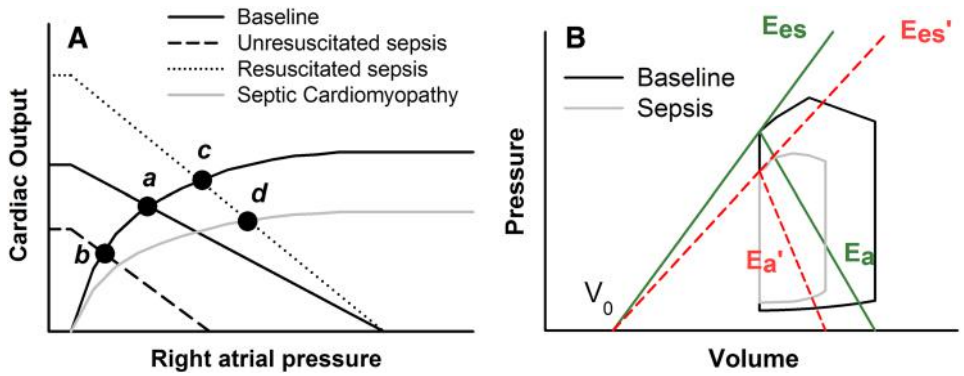

Fig. 1 **a** Interplay between venous return and cardiac function. The right atrial pressure at point *a* is the equilibrium point of venous return and cardiac function in a healthy circulation (*black line*). In unresuscitated sepsis (dashed line), the loss of stressed volume leads to a leftward shift of the venous return curve and a consecutive drop in cardiac output (point *b*), the decrease in resistance to venous return (inverse of the slope) cannot compensate. After volume resuscitation (*dotted line*), high cardiac outputs are possible (point *c*). If septic cardiomyopathy is present, cardiac output remains depressed despite volume resuscitation (point *d*). **b** Ventriculo-arterial decoupling in septic shock. Ventriculo-arterial coupling can be assessed as the ratio of the arterial elastance (E_a) divided by the end-systolic elastance of the ventricle (E_{es}). E_a is represented by the slope between the end-systolic pressure and the stroke volume, the end-systolic ventricular elastance E_{es} is reflected in the slope between the unstressed ventricular volume V_0 and the end-systolic pressure. E_{es} is the most load-independent parameter of ventricular contractility. Ratio values close to 1 (heart and circulation are coupled) describe an energetically favourable state where the arteries are apt to take the stroke volume. All pulsatile energy is transmitted to the arterial tree. Septic cardiomyopathy with diastolic dysfunction leads to increased ventricular filling pressures and a decrease in the end-systolic elastance (E_{es}'). The arterial elastance is relatively increased in the presence of excessive vasopressor load. This results in decoupling of the ventricle from the arterial tree with $-E_a'/E_{es}' > 1$. Figures adapted from [5] and [13]

[10]. Right ventricular (RV) dysfunction is common in patients with septic shock, especially in the presence of concomitant acute lung injury and mechanical ventilation [8]. Increased pulmonary vascular resistance, myocardial depression, and increased afterload due to mechanical ventilation all contribute to RV dysfunction and failure, and volume loading may further worsen it. RV dysfunction causes pulse pressure variation. Using pulse pressure variation to guide fluid administration in this context leads to further detrimental volume loading [11]. RV dysfunction can also mask relevant LV dysfunction, and should be considered in the presence of apparently poorly filled or hyperkinetic LV; LV dysfunction may only become evident after improved RV function.

Cardiac output may thus be compromised because of reduced venous return and dysfunction of either of the ventricles. Evaluation of both RV and LV and their diastolic and systolic function using echocardiography, and monitoring cardiac output responses to treatment guide optimum therapy [12]. Inotropes help to improve systolic function of both ventricles, whereas high doses of any adrenergic drugs can worsen diastolic dysfunction. If relevant myocardial dysfunction is present, volume should be administered with special care—the transition from beneficial to harmful increase in preload can be very rapid.

The ejection of both ventricles is influenced by their respective afterloads and thus the elastic properties of the systemic or pulmonary arterial trees. Ventriculo-arterial decoupling is mismatch between ventricular contractility and the vascular elastance (Fig. 1b) and may lead to an inefficient use of the mechanical energy that is provided by the heart. Both ventricles may become decoupled from their vascular trees in sepsis [13, 14]. The clinical relevance of ventriculo-arterial decoupling in circulatory failure in sepsis is poorly understood.

In conclusion, circulatory failure in sepsis results from a complex interaction of the circuit and the heart. Septic cardiomyopathy impairs the functions of both ventricles, and loss of stressed volume due to reduced vascular tone limits the venous return. The venous return is limited further if right atrial pressure increases more than MSFP. Therapeutic interventions aimed at restoring the stressed volume by judicious administration of volume and vasopressors may be limited by the dysfunction of either ventricle. Thus, therapeutic interventions aiming to restore stressed volume while avoiding unnecessary increases in right atrial pressure seem rational. Vasopressors should be used with caution since they may have detrimental effects on cardiac function and ventriculo-arterial coupling. This can be achieved by avoiding too ambitious mean arterial blood pressure goals. Volume state, vascular tone and cardiac performance are in close interaction—none of these components can be changed without consequences to the others. Hence, therapeutic interventions should be guided by the underlying physiology rather than targeted to predefined values of cardiac output or blood pressure [15].

Compliance with ethical standards

Conflicts of interest
The authors do not have any conflict of interest regarding this article.

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