Summary and conclusions

A fundamental challenge in septic shock resuscitation is to evaluate tissue perfusion. In this thesis, we review the basic foundations for the development of a comprehensive and holistic model for perfusion assessment in septic shock, and outline its application to evaluate the impact of resuscitation strategies on tissue perfusion.

1. In contrast to initial sepsis-related circulatory dysfunction, persistent circulatory dysfunction can be expressed in complex and heterogeneous patterns. Several recent studies support the heterogeneity of hemodynamic and perfusion profiles in persistent sepsis-related circulatory dysfunction. A conceptual framework for understanding the relationship between macrohemodynamics, and metabolic, peripheral and microcirculatory perfusion parameters is built up. This holistic approach is useful to develop monitoring algorithms that can aid in interpreting perfusion changes throughout septic shock resuscitation, particularly in determining the likelihood of a hypoxia-related mechanism in cases of persistent hyperlactatemia.

2. The maintenance of normal lactate levels in a septic patient with circulatory dysfunction is of great clinical and physiological interest. In fact, since several potential mechanisms can induce hyperlactatemia, including low cardiac output, microcirculatory abnormalities, sustained hyperadrenergia with accelerated aerobic glycolysis, and hepatosplanchnic hypoperfusion, among others, it is likely that the absence of hyperlactatemia reflects a more adequate physiological response to stress. In two studies involving 426 septic shock patients treated with perfusion-oriented algorithms, we demonstrated that one-third of them course without hyperlactatemia, exhibit an extremely low mortality, less organ dysfunctions and a better preserved microcirculatory flow, although they are indistinguishable in macrohemodynamic aspects. On the contrary, development of hyperlactatemia during persistent circulatory dysfunction is probably multifactorial but clearly represents an unbalanced physiological state.

3. Microcirculatory alterations, particularly proportion of perfused vessels and perfused vessel density, can be staged in severity and specific cut-offs related to mortality and morbidity can be identified (Chapters 2 and 5). Clinically relevant microcirculatory abnormalities are significantly more prevalent in patients with hyperlactatemia and requiring doses of norepinephrine >0.3 mcg/kg/min. Thus, these patients may constitute an appropriate target for microcirculatory-oriented resuscitation trials.

4. The fact that the majority of critically ill patients are mechanically ventilated may explain the uncommon finding of low ScvO₂ values in ICU patients. Since ScvO₂ is basically a superior vena cava regional monitor, its rapid improvement after the maneuver of sedation and mechanically ventilation may not assure a correction of global hypoperfusion.

5. Serial peripheral perfusion monitoring is a valuable tool to assess global resuscitation status. Capillary refill time is the earliest parameter in being normalized during septic...
shock resuscitation, and its normalization at 6 hours is significantly associated with a successful resuscitation at 24 hours.

6. High volume hemofiltration (HVHF) is a potential rescue therapy for severe hyperdynamic septic shock patients. Responders to this procedure decrease lactate levels and tend to improve microcirculatory abnormalities after a 12 h session. On the contrary, SvO₂ is almost normal at baseline and does not change during treatment in these severely ill patients, reflecting eventually a microcirculatory oxygen extraction deficit.

7. A multimodal perfusion-monitoring protocol was developed and applied to determine potential parameters associated to lactate clearance in a cohort of hyperdynamic septic shock patients with persistent hyperlactatemia. Impaired 6 h lactate clearance is associated to hepatosplanchnic hypoperfusion in some hyperdynamic septic shock patients subjected to aggressive early resuscitation. An improvement in systemic, metabolic, peripheral and even microcirculatory perfusion parameters does not rule out the persistence of hepatosplanchnic hypoperfusion.

8. Perfusion parameters exhibit markedly different recovery time courses in response to resuscitation in ultimately surviving septic shock patients. Some variables such as ScvO₂, P(cv-a) CO₂, CRT and StO₂ are already normal in more than 70% of patients six hours after starting ICU-based resuscitation. Lactate presents a biphasic recovery trend with a rapid significant decrease at 6 h, but a much slower recovery rate thereafter. Sublingual microcirculatory parameters exhibit the lowest recovery rate with persistent moderate derangements still present in almost 80% of patients at 24 h. These markedly different recovery time courses should be taken into account when composing a resuscitation protocol to avoid potentially harmful and inappropriate therapies.

9. Our multimodal perfusion-monitoring protocol can be applied to assess the efficacy of septic shock resuscitation strategies. When tested with this protocol, dobutamine fails to improve sublingual microcirculatory, hepatosplanchnic, peripheral perfusion parameters or lactate levels, despite inducing a significant increase in systemic hemodynamic variables.