Sepsis and septic shock are characterized by a low systemic vascular resistance/high cardiac output state, oxygen delivery is typically elevated. Nevertheless, despite this increased delivery of oxygen, tissue hypoxia persists in sepsis and contributes to organ injury. Microvascular dysfunction in sepsis has been extensively investigated in animals and humans. Sepsis results in derangements of microvascular flow, which can be identified very often in the early stages of this disease. Alterations of microcirculation are more severe in non-survivors, therefore it seems to be logical to target dysfunctional microcirculation. However, there is general failure of microcirculation protective interventions to improve clinical outcomes. Does it mean that we are on the completely wrong way? We do not have clear answer yet. Microvascular-protective strategies might probably be effective only in the patients who demonstrate baseline abnormalities of microvascular function. However, at present, we are not ready to specifically target the microcirculation in clinical routine outside studies. In the future, concepts for individualized hemodynamic optimization of both macrocirculation and microcirculation might constitute a new avenue to improve patients’ outcome. Supported by Ministry of Health of the Czech Republic, grant nr. 15-31881A. All rights reserved.