In a study in the previous issue of Critical Care, Thooft and colleagues [1] investigated the impact of increasing mean arterial pressure (MAP) by norepinephrine (NE) on systemic hemodynamics and organ perfusion in a series of patients with septic shock. The increase in MAP from 65 to 85 mm Hg was associated with increased cardiac output and mixed venous blood oxygen saturation (SvO₂) and a decreased blood lactate level. The increase in MAP was also associated with improvement of the microcirculation state as assessed by near-infrared spectroscopy (NIRS) at the thenar eminence level in 13 patients and by sidestream dark field (SDF) imaging at the sublingual level in 6 of them. NIRS technology allows investigators to evaluate the functionality of the thenar eminence microcirculation through the measurement of the muscle tissue oxygen saturation (StO₂) and its changes in response to a vascular occlusion test (VOT). SDF videomicroscopy allows investigators to assess the sublingual microvascular blood flow and capillary density by using several indices [2]. The presence of marked microvascular abnormalities detected by each of these techniques has been associated with increased mortality in septic shock [3,4].

Before being enrolled, the patients of Thooft and colleagues [1] had already been stabilized at an MAP of 65 mm Hg with fluid therapy and NE administration and their SvO₂ was above 65%, in accordance with Surviving Sepsis Campaign guidelines [5]. Although these goals appeared to have been achieved, severe derangements of organ perfusion were detected by both the NIRS and SDF techniques. This agrees with the concept that, in septic shock, microcirculatory abnormalities can persist despite apparent correction of macrocirculatory abnormalities [4,6,7]. However, it is still unclear whether the persistence of microcirculatory abnormalities at the early phase is related only to intrinsic septic organ/tissue injury or is a consequence of insufficient macro-hemodynamic resuscitation and, in particular, achievement of a still suboptimal organ perfusion pressure. Current recommendations suggest an MAP of at least 65 mm Hg given that, in patients with a history of hypertension or other vascular comorbidities or in those with increased abdominal pressure, a higher level of MAP may be required [5]. However, increasing the doses of NE carries the theoretical double risk of (a) decreasing cardiac output and oxygen delivery through an increased afterload effect and (b) worsening tissue perfusion through excessive peripheral vasoconstriction. Recent studies have evaluated the effects on cardiac output and organ...
perfusion markers of using NE to increase MAP from 60 (or 65) mm Hg to 85 (or 90) mm Hg in patients with septic shock [8-10]. All of the studies supported the idea that, in spite of the increase in cardiac output, achieving the upper MAP target is not always associated with a remarkable improvement in organ perfusion.

In contrast to previous studies, the study by Thooft and colleagues [1] demonstrated that an MAP target of 85 mm Hg might be more appropriate than 65 mm Hg for the microcirculation. One of the strengths of the study is that these results were found by using two different techniques: NIRS and SDF imaging. The higher StO2 reperfusion slope (during a VOT) at the highest level of MAP suggests that some degree of microvascular recruitment occurred at this level, confirming results found in patients with severely hypotensive sepsis [11]. In addition, increasing MAP from 65 to 85 mm Hg significantly improved two of the SDF-derived indices: the perfused vessel density and the microvascular flow index [1]. This suggests that both microvessel recruitment and microcirculatory blood flow increased at the MAP of 85 mm Hg. These findings can be the result either of a proper perfusion pressure effect in some pressure-dependent areas or of the increase in systemic blood flow observed at the highest level of MAP. The association of increases in cardiac output with NE-induced increases in MAP is a common finding that has been reported previously [8-13]. Clearly, the results of Thooft and colleagues [1] argue against the idea that, owing to excessive vasoconstriction, NE could exert deleterious effects on the microcirculation when an MAP of 85 mm Hg is targeted. It is important to note that 85 mm Hg is still low compared with MAP values of the healthy population [14], especially in the age group of the study by Thooft and colleagues [1].

Because the SDF analysis was conducted on only 6 of the 13 patients in the study by Thooft and colleagues [1], the interpretation of their data must be cautious. It must be underlined that, using study designs similar to that of Thooft and colleagues in the early phase of septic shock, Jhanji and colleagues [9] and Dubin and colleagues [10] reported no overall change in sublingual SDF-derived variables with NE-induced increases in MAP (above 60 mm Hg in 16 patients and 65 mm Hg in 20 patients, respectively). Nevertheless, Dubin and colleagues [10] reported an inverse correlation between the baseline level of the sublingual microcirculation state and the microcirculatory response to the NE-induced increase in MAP from 65 to 85 mm Hg. Thus, septic patients with normalized microcirculation (after initial hemodynamic resuscitation) might not benefit from any additional increase in MAP above 65 mm Hg. In contrast, septic patients with persistent altered microcirculation, though Surviving Sepsis Campaign recommended endpoints are achieved, might benefit from a further increase in MAP beyond the ‘magic’ value of 65 mm Hg. The results of Thooft and colleagues [1] are in agreement with this sensible concept, which clearly needs to be implemented in clinical practice.

This paper [1], like other recent ones [7,15,16], has the merit of bringing to light the idea that, at least during the early phase of sepsis, the microcirculation is not dissociated from the macrocirculation, despite what is claimed by pioneers of the microcirculation evaluation. More importantly, the paper suggests that bedside assessment of microcirculation might help clinicians to define the optimal level of macrocirculatory resuscitation targets (for example, MAP and SvO2) in each patient.

Abbreviations
MAP, mean arterial pressure; NE, norepinephrine; NIRS, near-infrared spectroscopy; SDF, sidestream dark field; StO2, muscle tissue oxygen saturation; SvO2, mixed venous blood oxygen saturation; VOT, vascular occlusion test.

Competing interests
The authors declare that they have no competing interests.

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