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EDITORIAL

Vasopressors in shock: are we meeting our target and do we really understand what we are aiming at?

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The rationale for the use of vasopressors in shock is twofold. First, in a rescue attempt, when arterial blood pressure drops below a critical threshold under which the heart and brain are hypoperfused, vasopressors are administered to restore arterial blood pressure back to levels that maintain coronary and cerebral perfusion, even if this potentiates peripheral vasoconstriction. Second, vasopressors are infused in the intention to reverse excessive vasodilatation in shock. Clinicians assume that systemic blood flow is then redistributed from the muscular, mesenteric, and cutaneous vascular beds to visceral and vital organs. Both in clinical practice [1, 2] and clinical trials [3, 4], mean arterial blood pressure (MAP) has been the primary parameter to guide resuscitation and titrate vasopressors in shock. However, it is increasingly acknowledged that using MAP as the main resuscitation endpoint in shock implies relevant limitations [5]. As MAP is, in simplified form, the mathematical product of cardiac output and vascular resistance, elevating MAP by increasing vascular resistance carries the detrimental risk of further compromising tissue perfusion in low cardiac output/high vascular resistance states. In addition, no clear relationship between MAP and microcirculatory blood flow has so far been established in patients with shock [6, 7]. Similarly, vasopressor-induced changes in MAP have had variable effects on capillary perfusion and single organ function in clinical studies [7]. Finally, it is unlikely that one specific resuscitation endpoint, instead of a physiology-based approach applying individualized endpoints and hemodynamic interventions, will be adequate for all patients in shock.

A recent systematic review identified only two randomized controlled trials comparing different MAP targets for titration of vasopressor drugs in septic shock [8]. In a new article in this journal, the Canadian Critical Care Trials Group presents the results of the OVATION (Optimal Vasopressor TItratiON) open-label randomized controlled trial (RCT) [9]. It was planned as a multicenter feasibility trial to inform the design of a larger study. Over a 16-month period, 120 out of 1017 screened and 238 eligible patients with vasodilatory shock were enrolled. Patients were randomized to vasopressor titration according to a target MAP range of 60–65 mmHg or one of 75–80 mmHg. A between group difference in MAP of at least 5 mmHg was used for sample size calculations, and with an observed difference of 9 mmHg (95 % CI 7–11 mmHg) the authors have to be congratulated that they could confirm the feasibility of their study.

However, four study findings deserve consideration. First, during approximately 70 % of the time observed MAP levels were out of the prescribed target MAP range with a mean observed MAP of 70 ± 5 mmHg in the lower and 79 ± 5 mmHg in the higher target MAP group. Notably, the majority of MAP 'outliers' were above the target range, in agreement with SEPSISPAM trial findings (mean MAP levels 73–78 mmHg in the 65–70 mmHg target MAP group and 82–87 mmHg in the 80–85 mmHg target MAP group) [10]. Clinical data (and experience) suggest that critical care staff rather considers target MAP range as the lower limit to increase vasopressor dose instead of using it as an upper limit to decrease it [3, 4, 10]. On the basis of previous study results, many intensive care nurses and physicians seem to consider a MAP between 70 and 85 mmHg as the 'comfort zone'. However, vasopressors may have serious

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Table 1 Issues to be addressed in future MAP trials in critically ill patients

1.	Universal MAP target/set point
	Is there an optimal MAP target/set point in vasodilatory shock/other shock types?
2.	Lower MAP with consideration to hypoperfusion
	Is permissive hypotension with consideration to hypoperfusion markers beneficial? If so, how low can we go? Which markers of hypoperfusion (tissue or organ) should we use?
3.	Subgroup effects
	Should MAP be targeted according to specific subgroups (chronic arterial hypertension, age, type of vasodilatory shock, necessary catecholamine support, etc.)?
4.	Vasopressor choice and MAP
	Does the optimal MAP depend on the choice of vasopressor(s)?
5.	Protocol adherence
	In order to increase the applicability of future findings, present issues with adherence to allocated MAP in RCTs need to be mitigated

MAP mean arterial blood pressure, *RCT* randomized controlled trial

adverse effects in critically ill patients with shock [10–12], and, therefore, titration of these agents to the lowest necessary dose may be beneficial. In contrast to the clinical trials mentioned above [9, 10], retrospective observational studies suggest that MAP levels between 60 and 65 mmHg can best predict survival from septic shock [13, 14]. Elevating MAP above 70 mmHg by intensifying vasopressor therapy was even associated with an increased risk of adverse events [11]. To allow for more definite conclusions, better compliance with the protocol and more data regarding concomitant interventions and actual hemodynamic values are needed in future trials (Table 1).

Another striking finding of this trial was that patients randomized to the 75–80 mmHg MAP range received 40 % higher vasopressor doses and were two additional days on vasopressor support than patients allocated to the lower MAP range, in line with the findings of the SEPSISPAM trial. An increased treatment intensity to achieve higher MAP levels did not only include vasopressor drugs but also blood transfusions (49 % in the lower and versus 71 % in the higher MAP group). Contrary to this finding, the SEPSISPAM trial found no indication of increased transfusions in the higher MAP group.

Third, the definition of vasodilatory shock in this study was not standardized and left to the judgement of the attending physicians. This may be problematic as vasodilatory shock summarizes a multitude of diseases. Even the largest subgroup of patients with vasodilatory septic shock may actually represent two distinct populations. Despite comparable macrohemodynamics, patients may relevantly differ in their lactate levels and thereby microcirculatory derangements, organ dysfunction, and mortality [15]. Various vasopressors and vasopressor combinations were administered. However, vasopressors differ in their pharmacology and safety profiles which makes interpretation and extrapolation of the study results difficult.

Finally, the subgroup analysis suggesting improved hospital survival in patients over 75 years and randomized to the 60–65 mmHg MAP range deserves notification. The age limit of 75 years appears arbitrarily chosen and not supported by strong biological plausibility. Additionally, the number of patients in this subgroup was inadequate ($n = 25$). The objective to identify a population at specific risk for adverse vasopressor effects is though clinically relevant. Observational studies have suggested that age per se is not an independent risk factor for the occurrence of adverse events during vasopressor therapy [11, 12], which emphasizes the need for large-scale RCTs with predefined subgroups and stratification by subgroup before any conclusions can be made. Instead, the intensity of vasopressor therapy and the disease severity may be the most relevant independent risk factors to predict complications. Because observational studies have their inherent bias, both treatment targets (including different MAP levels and other perfusion-based targets) and different treatments need to be tested in future randomized trials.

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Compliance with ethical standards

Conflicts of interest
None of the authors has a conflict of interest to declare.

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