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EDITORIAL

Focus on blood pressure targets and vasopressors in critically ill patients

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For patients in shock, decisions on blood pressure targets are an ongoing task for the clinicians at the bedside in critical care settings. In general, there are only limited amount of data from studies with lower risk of bias to support the clinicians in these decisions. However, in recent years, large cohort studies and randomised clinical trials (RCTs) have given us somewhat better data to support better care.

What blood pressure target is chosen will likely have important clinical implications, not only because different blood pressure targets may affect organ perfusion differently, but also because they require different dosing and choices of vasopressor agents. A delicate balance likely exists between the consequences of hypotension-induced hypoperfusion, on one side, and on the other side, the consequences of the interventions given, mainly vasopressors and their dosages and the duration of administration.

In a large registry study from 110 ICUs in the US, hypotension—as time-weighted averages—in patients with sepsis was associated with increased risk of myocardial injury, acute kidney injury and death [1]. For the two latter outcomes, the odds for worse outcome increased with decreasing mean arterial pressures (MAP) from 85 mmHg. This does not mean that we should apply 85 mmHg as the target for vasopressor therapy, because observational data cannot prove causality and any time-dependent interactions with interventions and any other physiological markers are very difficult to control for in such analyses [2–4]. In addition, registry data often contain few or no data on important clinical markers, in this case the simple markers of peripheral perfusion, which likely interacts with any effects of hypotension on mortality [5, 6]. Importantly, a recent individual patient data meta-analysis (IPDMA) of two RCTs [7, 8] of lower vs. higher blood pressure targets in ICU patients with shock suggested that no sub-groups were harmed from lower MAP targets [9]. If anything, two sub-groups of patients were harmed from a higher MAP target being patients with more than 6 h of vasopressor exposure before randomization and those aged 65 years or above. Taken together, clinical equipoise exists [10], and more RCTs on blood pressure targets in shock patients are underway, including the large 65-trial on permissive hypotension in patients aged above 65-year who have shock (ISRCTN10580502). The results of the 65-trial should be presented soon as enrolment has ended. Uncertainty may remain regarding the need to individualize blood pressure targets based on habitual blood pressure levels or the trajectory of critical illness, e.g., the phases of resuscitation, stabilization and recovery.

The choice of vasopressor to obtain the blood pressure target is also likely to matter. A recent multicenter, blinded RCT of the longer-acting vasopressin-analogue terlipressin, which has higher affinity for the V_{1a} receptor, showed no effect on the primary outcome 28-day mortality as compared with noradrenalin in patients with septic shock (Table 1) [11]. More serious adverse events were observed with terlipressin; more specifically, there were more patients with digital ischemia in the vasopressin-analogue group [11]. The accompanying editorial comment warned that care should be taken if this vasopressor is used [12]. In addition, these results may further support that noradrenalin should be the first line vasopressor in patients with shock [13].

The use of noradrenalin as compared to vasopressin (the endogenous hormone arginine-vasopressin, which is shorter acting than terlipressin) will likely result in

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Table 1 Larger randomized trials of vasopressin or its analogues vs. noradrenalin in critically ill patients

Trial	Registration	PICO	Sample size	Primary result	Serious adverse events
VASST	ISRCTN 94845869	P: septic shock I: vasopressin infusion C: noradrenalin infusion O: 28-day mortality	Planned 776, enrolled 778	28-day mortality 35% vs. 39%	10% vs. 11%
VANISH[a]	ISRCTN 20769191	P: septic shock I: vasopressin infusion C: noradrenalin infusion O: kidney failure free days at day 28	Planned 412, enrolled 421	Kidney failure free days at day 28, 9 vs. 13 days[b]	11% vs. 8%
Multicenter, prospective, randomized, controlled, double-blind study in China to evaluate the effect of terlipressin in patients with septic shock	NCT 01697410	P: septic shock I: terlipressin infusion C: noradrenalin infusion O: 28-day mortality	Planned 1000, enrolled 617	28-day mortality 40% vs. 38%	30% vs. 12%
SEPSIS-ACT	NCT 02508649	P: septic shock I: selepressin infusion C: noradrenalin infusion O: vasopressor- and mechanical ventilator-free days at day 30	Planned 1800[c], enrolled 868	Pending	Pending

PICO patients, intervention, comparator, outcome

[a] Bifactorial design with co-allocation to hydrocortisone vs. placebo

[b] Survivors who never developed kidney failure: vasopressin 57% and noradrenalin 59%

[c] Terminated for futility based on an interim analysis of the probabilities of final trial success

more episodes of atrial fibrillation as observed in a recent IPDMA [14]. Also, in this analysis, more episodes of digital ischemia were observed with vasopressin as compared to noradrenalin. While we await the publication of the largest RCT on vasopressin-analogues in septic shock, the SEPSIS-ACT trial on the short-acting V_{1a}-specific analogue selepressin [15] (Table 1), the cumulative evidence on the effects of vasopressin and its analogues vs. noradrenalin in patients with septic shock appears to be that the choice does not affect mortality (Table 1), the vasopressin and its analogues cause higher incidences of digital ischemia and noradrenalin causes higher incidences of atrial fibrillation. The choice between vasopressin and its analogues vs. noradrenalin may therefore rely on the risk for the specific patient for these adverse events, the costs of the agents and the knowledge of the staff who are to infuse and monitor the patient. However, simplification of care has rational in general and adding vasopressin as a second vasopressor in patients with shock adds additional complexity to the care of these patients.

A third vasopressor, angiotensin II, was recently tested as an add on to other vasopressors, mainly being combined noradrenalin and vasopressin, in 344 ICU patients with vasodilatory shock in the placebo-controlled ATHOS-3 trial [16]. Angiotensin II clearly increased blood pressure (the primary outcome) and decreased the administration of other vasopressors as compared with placebo. While no apparent differences in adverse effects were observed in the ATHOS-3 trial, angiotensin-II cannot be recommended in patients with shock given the limited safety data and the cost of this vasopressor.

An additional issue is the critically ill patients who have continued vasoplegia for a prolonged time-period. In these there may be a role for oral vasopressor treatment, e.g., midodrine, to promote liberation from central lines, mobilization, de-escalation of the monitoring level and ICU discharge [17, 18].

Finally, the results of the above studies do little in answering the more controversial question, should we target blood pressure at all? If our aim is to improve outcome through improved mitochondrial, cellular and/or tissue function, blood pressure may be a very distant marker to target? In any case, assessing different aspects of current clinical practice will improve the care of our patients while we await the results of the difficult clinical studies that may enlighten us about the better targets.

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Compliance with ethical standards

Conflicts of interest
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