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EDITORIAL

Hemodynamic targets in the initial resuscitation of older patients with sepsis: time for a reappraisal?

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The growing number of older patients requiring intensive care unit (ICU) admission has prompted increasing interest from clinicians and researchers in better understanding the specific needs of this population [1]. Beyond the question of ICU admission itself, the interventions administered in the ICU must also be evaluated. Among these, hemodynamic management and mean arterial pressure (MAP) targets have been studied, with evidence suggesting that elevated MAP targets may be harmful in patients aged 65 and older [2, 3].

In the multicenter, open-label randomized controlled trial OPTPRESS, Endo and colleagues [4] compared the effect of targeting a higher MAP (80–85 mmHg) *versus* a lower MAP (65–70 mmHg) in adult patients aged 65 years old and older with a diagnosis of septic shock. In both groups, vasopressin was initiated early, as soon as norepinephrine reached ≥ 0.1 µg/kg/min. Contrary to the authors' hypothesis—that a higher MAP would reduce mortality by 10%—the trial was stopped early for harm after an interim analysis involving 518 patients. Mortality at day 90 was significantly higher in the high-MAP group: 39.3% vs. 28.6% in the low-MAP group. The secondary outcomes—including ventilator-free days, catecholamine-free days, and renal replacement therapy–free days—also favored the lower MAP group. Importantly, there was no evidence of heterogeneity of treatment effect of hypertension status (interaction p-value = 0.27) for the observed harm.

The potential harm associated with targeting a higher MAP in older patients is a critical finding. Prior studies had already raised concerns in this context. An individual patient data meta-analysis of the OVATION and SEPSISPAM trials found an age-related increase in mortality risk when a high MAP was targeted [2, 5]. More recently, Lamontagne et al. demonstrated that a permissive hypotension strategy (MAP target between 60 and 65 mmHg) in patients over 65 years old with vasodilatory shock possibly improved survival (HR 0.94, 95%CI 0.84–1.05), with a counterintuitive favorable heterogeneity of treatment effect among patients with chronic hypertension (OR = 0.67, 95%CI 0.51–0.88, interaction p value = 0.047) [3]. The current study reinforces these findings in a more homogeneous population of patients with septic shock.

The harmful effects of higher MAP targets are likely linked to the adverse effects of vasopressors. Both norepinephrine and vasopressin doses were higher in the high-MAP group. The increased need for norepinephrine in achieving higher MAP targets is well established [6] as is its potential contribution to poor outcomes through various side effects, supporting strategies aimed at minimizing catecholamine use [7].

In OPTPRESS, the authors employed a vasopressin-based catecholamine-sparing strategy to achieve the high-MAP target, which may explain the differences in the adverse events profile when compared to the SEPSISPAM trial (which had shown a higher risk of arrhythmias) [6]. While current guidelines support vasopressin as a catecholamine-sparing agent [8], the optimal timing and method of its use remains uncertain [9].

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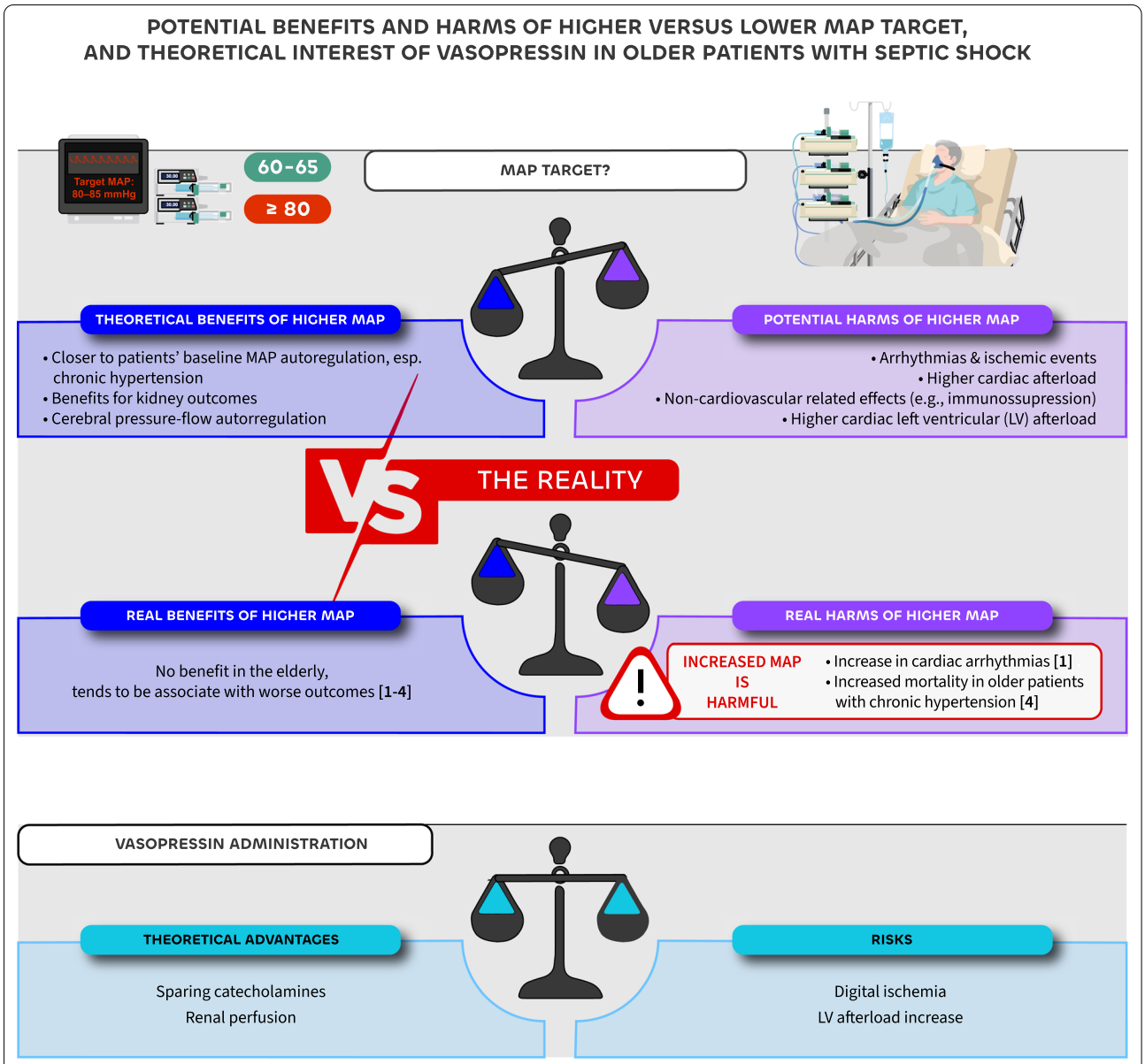

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Fig. 1 Potential benefits and harms of higher versus lower MAP target, and theoretical interest of vasopressin in older patients with septic shock

As vasopressin exerts an exclusive vasoconstrictive effects via V1a receptors without beta-adrenergic stimulation, left ventricular afterload increases [10], which may be particularly harmful in older patients with impaired cardiac function. Adequate assessment of the cardiac function in this scenario is, therefore, needed to avoid adverse effects (Fig. 1).

As in many trials on MAP targets, actual MAP values achieved were often higher than expected [3, 6], but this observation should not overshadow a more fundamental issue: clinicians must consider not only the MAP value itself, but its physiological consequences. The goal of early resuscitation is to restore tissue perfusion and prevent the circulatory, cellular, and metabolic abnormalities that lead to organ failure [11]. However, during septic shock, macro and microcirculation dissociation is one of the key features of its pathophysiology [12].

Taken together, one point of view is that the results of OPTPRESS and other trials testing MAP targets suggest that vasodilatation is likely an adaptive response that should be cautiously corrected to a minimum extent in clinical practice. Correcting it with the sole aim of achieving higher MAP targets, even among previously hypertensive patients, is likely harmful and should be avoided in clinical practice. Whether vasopressor test strategies targeting perfusion are beneficial should be the focus of future research in both older and younger patients. This requires an integrated approach that considers both macro- and microcirculatory responses, as proposed by Hernandez et al. [13].

Several key considerations must be addressed in the management of older patients with septic shock, reflecting their physiological complexity and comorbidities:

- Restoring perfusion rapidly, while accounting for potential cardiac dysfunction. The general recommendation of rapid administration of 30 ml/kg of crystalloids should be specially tailored to cardiac reserve and fluid tolerance.

- Choosing the appropriate vasopressor and its timing according to the premorbid conditions and a comprehensive assessment of cardiovascular function.

- Managing persistent hypoperfusion after initial resuscitation considering a time-limited "vasopressor test"—a brief MAP increase—to assess reversibility of tissue perfusion. Identification of meaningful markers to guide this approach (e.g., capillary refill time, urine output, lactate clearance) remains a major challenge.

Every now and then, we are reminded of the importance of conducting clinical trials in critical care. This is one such situation. The authors of OPTPRESS should be commended for conducting this trial and for their substantial contribution to the evidence base to better care for our patients. Now, we hope upcoming trials targeting perfusion—not pressure—may answer whether individualizing macrohemodynamic strategies to target perfusion will be the way forward in septic shock resuscitation [14].

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Declarations

Conflict of interest
Ricard Ferrer is a Deputy Editor for Intensive Care Medicine journal. Other authors declare to have no conflicts of interest in relation with this manuscript.

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Not applicable.

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