Intensive Care Med
https://doi.org/10.1007/s00134-018-5292-8

EDITORIAL

MAP of 65: target of the past?

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Septic shock is defined as sepsis with hypotension refractory to fluid challenge and requiring vasopressor support combined with an increase in arterial lactate reflecting impaired cellular energy metabolism and dysoxia. The use of vasoactive drugs to restore mean arterial pressure (MAP) is strongly recommended by the Surviving Sepsis Campaign [1] and the Task Force of the European Society of Intensive Care Medicine (ESICM) on circulatory shock management and monitoring [2].

Resuscitation in septic shock aims to restore tissue perfusion pressure without excessive vasoconstriction, which impedes flow and paradoxically worsens organ dysfunction or leads to other adverse events. MAP is a key component of tissue perfusion and is often viewed as a surrogate of organ perfusion pressure. Both the SSC and ESICM guidelines suggest keeping MAP $\geq$ 65 mmHg and individualizing this target based on comorbidities.

The current MAP target of 65 mmHg is mainly based on the results of two retrospective studies investigating sequential MAP readings and the time spent below different threshold values of MAP during the first 24 or 48 h of management of patients with septic shock [3, 4]. Both studies showed a correlation between MAP thresholds and survival [3, 4] and organ dysfunction [4, 5]. Best results were seen with a MAP between 60 and 65 mmHg, and the time spent below these values correlated with risk of mortality [3, 4]. There was no survival benefit with higher MAP thresholds. Furthermore, the risk of mortality increased markedly in patients treated with high doses of norepinephrine irrespective of the MAP [5]. Recently, two prospective randomized controlled trials, SEPSISPAM and Ovation, compared high versus low target MAP on chances of survival in patients with septic shock [6, 7]. In SEPSISPAM, patients were enrolled within 6 h of initiation of vasoactive drug treatment. In OVATION, patients were recruited up to 24 h after the diagnosis of septic shock. Target values were 80–85 vs. 65–70 and 75–80 vs. 60–65 mmHg for the high vs. low MAP in SEPSISPAM and OVATION, respectively. There was no significant survival difference between the treatment groups at day 28 in either trial. However, both trials were underpowered as the mortality rate in the control groups was lower than expected. In addition, patients assigned to the low MAP target groups achieved higher MAPs than planned according to the study protocol.

In a recent article in Intensive Care Medicine, Maheshwari et al. report the results of a retrospective analysis of 8782 patients admitted to 110 US hospitals exploring the association between MAP and acute kidney and myocardial injury as well as in-hospital mortality in patients with septic shock [8]. Using routinely collected data from an electronic health records database, the authors defined total exposure to hypotension as the time-weighted average mean arterial pressure (TWA-MAP) and calculated the cumulative time spent below 55, 65, 75, and 85 mmHg thresholds. The main results were that (1) exposure to hypotension of TWA-MAP below 65 mmHg was directly related to hospital mortality, (2) the longer the time spent below MAP 65 mmHg, the higher the risk of mortality, acute kidney and myocardial injury, and (3) risks for mortality, acute kidney injury, and myocardial infarction were apparent at 85 mmHg.

While the strengths of this study are the large number of patients from many hospitals in the US, potential weaknesses are the retrospective design with the associated risk of bias, the reliance on routinely collected data with variable time intervals between blood pressure measurements, and the lack of data on adverse effects of the treatments. In addition, it was not possible to discriminate between patients in whom hypotension was accepted (permissive hypotension) vs. hypotension

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refractory to vasoactive drugs. Finally, due to the nested design, the impact of higher MAP resuscitation in patients with septic shock was influenced by the lowest threshold. Definitively, this study was not designed to answer the question of the best MAP target.

To date, all studies included in the current international guidelines suffer from similar limitations [3]. Importantly, they were also relatively small with < 500 patients included. Despite these limitations, a target MAP of 65 mmHg is strongly recommended, especially since there was no evidence at the time that higher MAP thresholds were associated with better outcomes.

The data by Maheshwari et al. challenge current practices. The authors found a direct, statistically significant association between MAP and in-hospital mortality. It is obviously important to keep in mind that any potential beneficial effect of raising the MAP target should be balanced with potentially undesired side effects from vasoactive medications. Given the limitations of retrospective studies, the task of determining the optimal MAP for patients with septic shock will require adequately powered randomized controlled trials integrating age, gender, and preexisting comorbidities, i.e., more individualized treatment strategies [9].

Recent data suggest that mean perfusion pressure (MPP) may serve as a better surrogate marker of perfusion pressure than MAP. It is calculated as the difference between systemic mean arterial pressure (MAP) and CVP, i.e., MPP = MAP − CVP [10, 11]. Whether MPP is a better resuscitation target for patients with shock is unknown. It is also unclear whether different organ-specific perfusion targets are needed.

Until more data are available, the current recommendation of a target MAP of 65 mmHg during critical illness should be viewed with caution.

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Received: 15 June 2018 Accepted: 29 June 2018
Published online: 12 July 2018

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME et al (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43(3):304–377
2. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL et al (2014) Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 40(12):1795–1815
3. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki L-M, Pettilä V (2005) Hemodynamic variables related to outcome in septic shock. Intensive Care Med 31:1066–1071
4. Dünser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S, Daudel F, Lepper P, Hasibeder WR, Jakob SM (2009) Arterial blood pressure during early sepsis and outcome. Intensive Care Med 35:1225–1233
5. Dünser MW, Ruokonen E, Pettilä V, Ulmer H, Torgersen C, Schmittinger CA, Jakob S, Takala J (2009) Association of arterial blood pressure and vasopressor load with septic shock mortality: a post hoc analysis of a multicenter trial. Crit Care Lond Engl 13:R181
6. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N et al (2014) High versus low blood-pressure target in patients with septic shock. N Engl J Med 370(17):1583–1593
7. Lamontagne F, Meade MO, Hebert PC, Asfar P, Lauzier F, Seely AJ, Day AG, Mehta S, Muscedere J, Bagshaw SM et al (2016) Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentrepilot randomized controlled trial. Intensive Care Med 42(4):542–550
8. Maheshwari K, Nathanson BH, Munson SH, Khangulov V, Stevens M, Badani H, Khanna AK, Sessler DI (2018) The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med 44:857–867. https://doi.org/10.1007/s00134-018-5218-5
9. Saugel B, Vincent JL, Wagner JY (2017) Personalized hemodynamic management. Curr Opin Crit Care 23(4):334–341
10. Panwar R, Lanyon N, Davies AR, Bailey M, Pilcher D, Bellomo R (2013) Mean perfusion pressure deficit during the initial management of shock—an observational cohort study. J Crit Care 28(5):816–824
11. Ostermann M, Hall A, Crichton S (2017) Low mean perfusion pressure is a risk factor for progression of acute kidney injury in critically ill patients—a retrospective analysis. BMC Nephrol 18(1):151