Critical Care and Resuscitation 27 (2025) 100101

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Editorial

Excessive vasopressors or excessive hypotension: Searching for the goldilocks zone in mean arterial pressure targets

Keywords:
Mean arterial pressure
Vasopressors
Intensive care medicine
Critical care
Noradrenaline
Septic shock

Untreated, severe hypotension rapidly results in end-organ hypoperfusion and death.[1] Vasopressors are effective at increasing blood pressure; therefore, the infusion of vasopressors to avoid hypotension is a key intensive care unit (ICU) therapy.[2] Current guidelines suggest targeting a mean arterial pressure (MAP) of 65 mmHg in adults with septic shock.[3] Despite this MAP levels in ICU, patients receiving vasopressors often exceed this and recent evidence suggests that, compared to usual practice, targeting a lower MAP, effectively minimising exposure to vasopressors, may reduce mortality in patients with vasodilatory shock.[4,5]

1. Balance of risk

Whenever vasopressors are administered, a patient can potentially be exposed to an 'excess of hypotension' or an 'excess of vasopressor' (Fig. 1). As a conventional 'usual care' approach to treating hypotension involves targeting a higher MAP than a more permissive approach, where a lower MAP is accepted, it logically follows that ICU clinicians implementing a usual care paradigm may effectively be overestimating the mortality risk attributable to mild hypotension and underestimating the mortality risk attributable to exposure to vasopressors. While clinicians may be most concerned about vasopressor toxicity when doses of vasopressors are high, reducing exposure to vasopressors may still be important when vasopressor doses are low. In general terms, it is possible that whenever vasopressors are used to augment MAP, reducing exposure to an excess of vasopressor drugs is *at least* as important as minimising exposure to an excess of hypotension. The possibility that optimising the MAP by targeting a Goldilocks zone that minimises opposing risks of hypotension and vasopressor excess might reduce mortality has profound public health implications. Millions of patients are treated with vasopressors every year.

2. Current evidence

Despite recent evidence, the optimal MAP target for adults receiving vasopressor infusions remains uncertain. Numerous randomised clinical trials (RCTs) have compared two different MAP targets in specific populations, with no single study providing practice-defining evidence.[5–9] Several systematic reviews have been conducted with mixed results.[10–13] A recent individual patient data meta-analysis from three RCTs demonstrated a high probability of lower mortality from low MAP targets than from high MAP targets in critically ill patients with vasodilatory shock.[4] Conservatively, existing data evaluating MAP targets do not exclude clinically important effects of minimum MAP targets on mortality. Furthermore, the generalisability of current evidence is limited by its focus on patients with vasodilatory shock, particularly patients older than 65 years, a group not representative of the broad array of patients who receive vasopressors in clinical practice.

3. Possible heterogeneity of treatment effect

Data suggest the possibility of heterogeneity in the treatment effect in the patients included in clinical trials.[4,5] It is possible that the optimal minimum MAP target is dependent on the clinical context and varies over time. Data suggesting treatment effect heterogeneity come from traditional one-group-at-a-time subgroup analyses, but it is plausible that the determinants of optimal blood pressure are more complex than can be accounted for by such analyses. Recent techniques to determine individualised treatment targets accounting for all baseline variables seem ideally suited to defining the optimal approach to targeting MAP.[14,15] Given the many factors that may contribute to variability, randomising a large number of participants to several different targets is a likely prerequisite to determining the optimal approach.

A related issue is that existing MAP target trials compare two targets or one target vs. usual care. Evaluating MAP targets over the range of clinically acceptable levels may be necessary to provide the data required to optimise the target for individual patients.

4. Discrepancy between achieved and targeted MAP

An additional challenge with interpreting trials of MAP targets is that the MAP achieved often exceeds the targeted pressure.[5,8,9] A similar discrepancy between the prescribed MAP and the observed MAP is also seen in clinical practice.[16] It is unclear whether this discrepancy is because clinicians place greater weight on the importance of avoiding periods where MAP is transiently lower than intended than on avoiding periods where the dose of a vasopressor is greater than it needs to be. An alternative or additional explanation may be that the use of lower-limit monitor alarms

https://doi.org/10.1016/j.ccrj.2025.100101

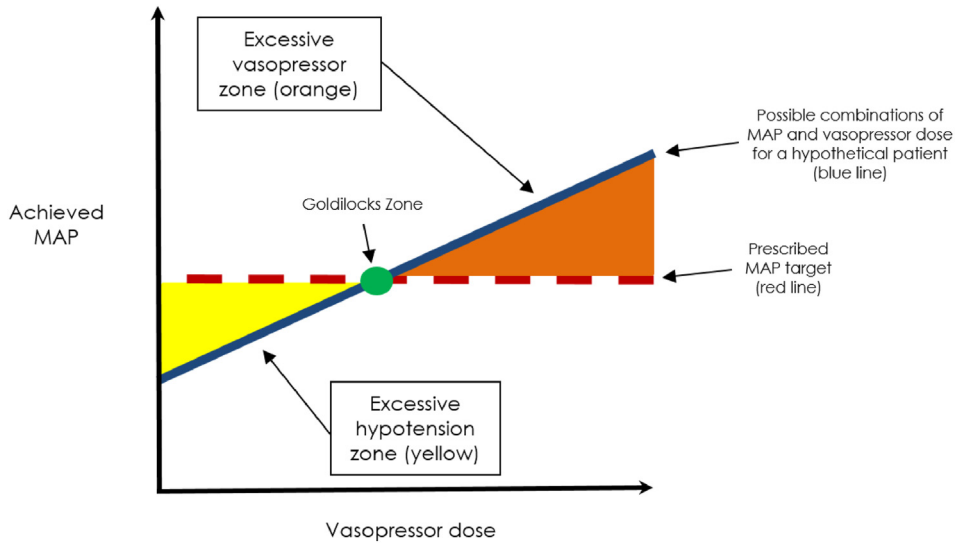

Fig. 1. Potential trade-offs between the dose of vasopressors and the dose of hypotension required when administering vasopressors in the ICU
Abbreviations: ICU: intensive care unit; MAP: mean arterial pressure.

leads nurses to titrate vasopressors to provide a buffer that avoids alarms sounding frequently.

5. Rationale for a Mega trial

Given existing evidence and ongoing uncertainty, the case for further clinical trials to evaluate the optimal approach to this common therapy overall and to optimise MAP targets for individuals is overwhelming. Instead of conducting multiple MAP target trials that assess specific patient groups, an alternative strategy would be to conduct an inclusive Mega mean arterial pressure (MEGA-MAP) trial across a broad population. The high level of inclusive recruitment to an intervention widely applicable to the patient population should create familiarity and efficiencies for clinicians and researchers in trial conduct. Furthermore, large recruitment numbers allow for the detection of small but clinically meaningful differences. The success of the mega randomised oxygen (MEGA-ROX) trial program in recruiting more than 1000 patients a month when evaluating titration oxygen therapy targets suggests that a similar trial of MAP targets may be feasible,[17] and a recent international survey of over 300 critical care clinicians showed a willingness to participate in such a trial.[18]

6. Specific issues to consider in the design of a MEGA-MAP trial

Several issues need to be considered in the design of a MEGA-MAP trial to investigate the optimal minimal MAP in critically ill patients receiving vasopressors.

Firstly, developing a strategy to overcome or minimise the discrepancy between prescribed and observed MAP is essential to ensure that each target MAP effectively balances the potential risks of excessive hypotension and excessive vasopressor doses. This may be achievable by using both lower-limit MAP alarms and tight upper-limit alarms. An alternative or additional means of doing this may be using a closed-loop vasopressor titration system where the vasopressor infusion rate is automatically adjusted in response to the MAP. Whatever strategies are employed data from a pilot RCT are likely to be required to confirm treatment-group separation in MAP and exposure to vasopressors.

Secondly, a clinical trial investigating MAP must be adaptable to the clinical context. For example, with escalating vasopressor dose, the magnitude of individual risks from either hypotension or vasopressor may change.[19] Another example of the need to be adaptable would be in situations of impaired end-organ perfusion where clinicians may consider there is a strong reason to adjust the MAP target. In such a situation, allowing the default minimum MAP to be altered by the treating clinician may be desirable. These situations and the probable heterogeneity of treatment highlight that a static, one-size-fits-all approach to MAP targets may not be viable.

A pilot RCT trial may help better define potential barriers to proposed interventions and would determine feasibility.

7. Conclusion

Titration of vasopressors to increase MAP is a fundamental ICU therapy that is delivered to millions of patients every year. A large-scale MEGA trial to determine the Goldilocks Zone that balances the risks of hypotension and vasopressor excess in critically ill patients and establishes whether this differs based on the clinical circumstances is a high priority.

CRediT authorship contribution statement

Young: Conceptualisation, Writing – Original Draft preparation. **White:** Writing – Reviewing and Editing.

Funding

Paul Young declares he is a member of the Editorial Board for *Critical Care and Resuscitation*. This research was conducted during the tenure of a Health Research Council of New Zealand Clinical Practitioner Fellowship held by Paul Young. The Medical Research Institute of New Zealand is supported by Independent Research Organisation funding from the Health Research Council of New Zealand.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paul Young declares he is a member of the Editorial Board for Critical Care and Resuscitation. This research was conducted during the tenure of a Health Research Council of New Zealand

Clinical Practitioner Fellowship held by Paul Young. The Medical Research Institute of New Zealand is supported by Independent Research Organisation funding from the Health Research Council of New Zealand.

References

[1] Maheshwari K, Nathanson BH, Munson SH, Khangulov V, Stevens M, Badani H, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med 2018;44:857–67.
[2] Vincent JL, Annoni F. Vasopressor therapy. J Clin Med 2024;13(23):7372.
[3] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–247.
[4] Angriman F, Momenzade N, Adhikari NKJ, Mouncey PR, Asfar P, Yarnell CJ, et al. Blood pressure targets for adults with vasodilatory shock - an individual patient data meta-analysis. NEJM Evid 2025;4(1):EVIDoa2400359.
[5] Lamontagne F, Richards-Belle A, Thomas K, Harrison DA, Sadique MZ, Grieve RD, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. JAMA 2020;323(10):938–49.
[6] Grand J, Meyer AS, Kjaergaard J, Wiberg S, Thomsen JH, Frydland M, et al. A randomised double-blind pilot trial comparing a mean arterial pressure target of 65 mm Hg versus 72 mm Hg after out-of-hospital cardiac arrest. Eur Heart J Acute Cardiovasc Care 2020;9(4_suppl):S100–9.
[7] Jakkula P, Pettila V, Skrifvars MB, Hastbacka J, Loisa P, Tiainen M, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med 2018;44(12):2091–101.
[8] Lamontagne F, Meade MO, Hebert PC, Asfar P, Lauzier F, Seely AJE, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive Care Med 2016;42(4):542–50.
[9] Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370(17):1583–93.
[10] Yoshimoto H, Fukui S, Higashio K, Endo A, Takasu A, Yamakawa K. Optimal target blood pressure in critically ill adult patients with vasodilatory shock: a systematic review and meta-analysis. Front Physiol 2022;13:962670.
[11] Sarkar S, Singh S, Rout A. Mean arterial pressure goal in critically ill patients: a meta-analysis of randomized controlled trials. J Clin Med Res 2022;14(5):196.
[12] Hylands M, Moller MH, Asfar P, Toma A, Frenette AJ, Beaudoin N, et al. A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anaesth 2017;64(7):703–15.
[13] D'Aragon F, Belley-Cote EP, Meade MO, Lauzier F, Adhikari NK, Briel M, et al. Blood pressure targets for vasopressor therapy: a systematic review. Shock 2015;43(6):530–9.
[14] Buell KG, Spicer AB, Casey JD, Seitz KP, Qian ET, Graham Linck EJ, et al. Individualized treatment effects of oxygen targets in mechanically ventilated critically ill adults. JAMA 2024;331(14):1195–204.
[15] Angus DC, Chang CH. Heterogeneity of treatment effect: estimating how the effects of interventions vary across individuals. JAMA 2021;326(22):2312–3.
[16] White KC, Quick L, Durkin Z, McCullough J. Mean arterial pressure in critically ill adults receiving vasopressors: a multicentre, observational study. Critical Care and Resusciation 2025.
[17] Young PJ, Arabi YM, Bagshaw SM, Bellomo R, Fujii T, Haniffa R, et al. Protocol and statistical analysis plan for the mega randomised registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX). Critical Care and Resuscitation 2022;24(2):137–49.
[18] Young P, Bellomo R, Abdulrahman A. Mean arterial pressure targets in ICU patients receiving noradrenaline: an international survey. Crit Care Resusc 2025. In Press.
[19] D'Amico F, Marmiere M, Monti G, Landoni G. Protective hemodynamics: C.L.E.A.R.! J Cardiothorac Vasc Anesth 2025;39(1):13–9.

Paul J. Young, FCICM, PhD*
Intensive Care Unit, Wellington Hospital, Wellington, New Zealand

Medical Research Institute of New Zealand, Wellington, New Zealand

Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia

Department of Critical Care, University of Melbourne, Melbourne, Victoria, Australia

Kyle C. White, FCICM, MPH
Intensive Care Unit, Princess Alexandra Hospital, Woolloongabba, Australia

Intensive Care Unit, Queen Elizabeth II Jubilee Hospital, Coopers Plains, Australia

School of Clinical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia

* Corresponding author.
E-mail address: paul.young@ccdhb.org.nz (P.J. Young).

3 February 2025