Commentary

The quest for the optimal blood pressure in septic shock

Sahajal Dhooria, Inderpaul Singh Sehgal, Ritesh Agarwal

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Correspondence to: Dr. Sahajal Dhooria, MD, DM. Assistant Professor, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh-160012, India. Email: sahajal@gmail.com.

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Septic shock is essentially characterized by reduced tissue perfusion due to distributive shock as a consequence of infection. One of the essential components in its management is restoration of tissue perfusion (1). To achieve this goal, one of the first steps is fluid resuscitation followed by the use of vasopressors, if required, in order to maintain tissue perfusion pressure. As perfusion of the vital organs cannot be gauged directly, one of the most commonly used surrogates is the mean arterial pressure (MAP), as it can be measured easily.

In the steady state, organ perfusion is determined by autoregulatory mechanisms and is not dependent on the arterial pressure (2). When the perfusion pressure (the difference between the inflow and outflow pressures) of an organ is allowed to fall below its autoregulation threshold, as occurs in septic shock, blood flow drops linearly with the decrease in the MAP. Maintaining MAP above the regulatory thresholds of vital organs such as the brain, heart, liver and splanchnic circulation, and the kidneys therefore becomes essential to ensure perfusion of these organs. The autoregulatory thresholds of vital organs have a broad range. While the autoregulation threshold for the brain may be between 60 and 85 mmHg, that for the kidneys is between 65 and 80 mmHg (3-6). The thresholds for the heart and the gut also fall in similar ranges. A study in an animal model suggests that while targeting a lower MAP was associated with a higher risk of acute kidney injury, a higher MAP target resulted in increased net positive fluid balance and vasopressor load during resuscitation (7). An observational study demonstrated improvement in renal perfusion when the MAP was increased from 65 to 75 mmHg, but no further improvement in renal perfusion was elicited, when the MAP was further increased to 85 mmHg (8). It is plausible that there are other factors at play that define the organ-specific autoregulation thresholds in individual patients, the most appealing (both according to physiology and the evidence) being the basal blood pressure before the acute illness. Thus, patients with uncontrolled hypertension may have higher autoregulatory thresholds and thus a need to maintain a higher MAP (9). While a higher MAP may be required for adequate organ perfusion, the use of vasopressors to achieve it is also associated with detrimental effects such as increased risk of arrhythmias and even increased mortality, especially when there is an abrupt and sustained increase in MAP (10). A high vasopressor load strains the heart and excessive vasoconstriction can cause reduced organ perfusion of some vascular beds, such as the skin and the gut (11-13).

In this backdrop, an important question that arises is whether there is an ideal target for MAP for all patients with septic shock and if yes, what is it? The Surviving Sepsis Guidelines recommend that a MAP of 65 mmHg should be the initial target and vasopressors should be used if this target is not met after adequate fluid resuscitation (generally 30 mL/kg body weight) (1). These recommendations are based on some evidence that MAP <60–65 mmHg is associated with poor outcomes (14,15). The guidelines further state that the MAP target needs to be individualized, as the MAP requirement may be higher for individuals with uncontrolled hypertension and lower in young, previously healthy individuals. In a recent multicenter, randomized, open-label, prospective study involving 776 septic shock patients (the SEPSISPAM trial), Asfar *et al.* have shown that targeting a MAP of 65–70 or 80–85 mmHg is equivalent in terms of mortality (9).

Lamontagne *et al.* have now reported in the journal *Intensive Care Medicine*, the results of the Optimal Vasopressor Titration (OVATION) pilot trial conducted

with an aim to inform the design of a larger trial examining the effect of lower versus higher MAP targets for vasopressor therapy in shock (16). The authors have assessed the feasibility of a randomized trial comparing lower MAP targets than those in the SEPSISPAM trial. In this study, 118 subjects with vasodilatory shock were enrolled from 11 centers and were assigned to a lower (60–65 mmHg) versus a higher (75–80 mmHg) MAP target. The primary objective of maintaining a between group separation in MAP [9 mmHg (95% CI, 7–11)] was achieved. No difference in the hospital mortality or the risk of arrhythmias was observed. Among subjects aged 75 years or older, lower hospital mortality was observed in the lower MAP group. While the study has strengths, it fails to address several important issues that are vital, in the light of the current state of knowledge on this topic.

If we look at the SEPSISPAM study, we find that it was well conducted, and gives us reason to believe that the lower and higher MAP targets may result in similar outcomes in the general population of septic shock patients (9). For a future trial addressing a similar issue, it would be important not only to avoid the limitations of the SEPSISPAM trial, but also build upon the insights gained from the exploratory analyses. A subgroup analysis in the SEPSISPAM trial suggested that the requirement of renal replacement therapy was higher in patients with a prior history of chronic hypertension assigned to the low MAP group. In this regard, the study by Lamontagne *et al.* does well to predefine important subgroups, such as that based on age, history of chronic hypertension, and congestive heart failure. The authors have also rightly performed analyses based on tests for interaction for the different subgroups that are more appropriate than treatment comparisons within the subgroups (17). However, it would have been better to perform stratified randomization according to the predefined subgroups, a point that was taken care of in the SEPSISPAM trial. In large trials, randomization ensures homogenization of the baseline risk in the different treatment groups, but this cannot be assumed in subgroups, if randomization is not appropriately stratified (18). The drawback of the lack of randomization was evident, as subjects with history of chronic hypertension were unequally distributed between the study groups in the OVATION study (16). Apart from randomization, it would also be important to have sufficient power to detect a difference in mortality in the subgroup of patients with chronic hypertension. Information about the premorbid blood pressure records, wherever available might also be collected and presented.

One of the important limitations of the SEPSISPAM study was that the actual achieved MAP was about 75 mmHg in the low MAP group, while the target range was 65–70 mmHg. The OVATION trial suffers from the same drawback of the actual mean MAP achieved being off the target in the low MAP group (70 mmHg as compared to a target range of 60–65 mmHg). Further, almost 70% of the hourly MAP measurements were off the target in either group. About 60% of the times, the actual MAP was higher than the target range in the lower MAP group. Thus, while the study confirms feasibility of adequately separating the average MAP in the higher and lower target groups (again similar to that achieved in the SEPSISPAM trial), it does not ensure the feasibility of keeping the MAP within the actual target range. Therefore, a crucial fact that emerges from these studies is that the actual MAP achieved may be different from what is targeted, even in a controlled setting of a randomized trial. While translating the evidence into clinical practice, if an average MAP of 60–65 mmHg is truly achieved, there is a high chance that it will be associated with periods of MAP lower than 60 mmHg, and other periods with MAP above 65 mmHg. The critical care physician in the intensive care unit needs to be cautious in this regard, as there is some evidence that the longer the duration of MAP remaining below 60 mmHg, higher is the mortality (19).

In a future study, comparison of a strategy of individualizing MAP targets versus fixed targets is rather needed. Individualization does not imply doing away with protocols; it rather means, having an elaborate protocol of fluid and vasopressor adjustments rather than blindly targeting a single value. For assessing organ perfusion, additional assessments such as measurement of the blood lactate levels, urine output, mental status, and skin perfusion are essential, as is the MAP target (1). Individualized therapy in research studies must also include assessments of microcirculation, so that the implication of the monitoring information these novel techniques, such as laser Doppler flowmetry, sidestream darkfield imaging, and near-infrared spectroscopy provide, can be better understood (20,21). At present, it is premature to set any definite microcirculatory targets in septic shock.

Further, as pointed out correctly in the past, the consideration of intra-abdominal pressure is necessary to calculate the actual renal perfusion pressure, which is missing from all these studies on blood pressure targets (6,22). Also, there is significant variability in the use of fluids and vasopressors across randomized controlled trials that may influence the outcomes (23,24). With this variability, it is even more difficult to attribute the outcomes to a single change in the MAP target. Further, the choice

of vasopressors and the optimal vasopressor dosing strategy also needs to be clearly defined (25,26). Although Lamontagne *et al.* have studied functional autonomy at six months, other long term outcomes including effects on neurocognitive function and sleep need to be addressed (27).

The effects of the MAP per se and the cumulative doses of vasopressors also need delineation. The norepinephrine load received in the high MAP groups of the studies is more likely to lead to adverse events including arrhythmias and mortality than the higher MAP per se. Avoiding confounding in this regard is difficult, if not impossible. On the one hand, while achieving a higher MAP may not be easy in patients with severe illness with refractory shock, it may further result in higher doses of vasopressors being used which, in turn, may adversely affect the outcomes. Thus, the effects of the severity of the disease, the MAP target, and the vasopressor load on the outcome cannot be separated, as the three are interlinked.

In conclusion, trials comparing MAP targets in septic shock may not reveal a difference in survival in the general population of septic shock patients; however, they may highlight survival differences in certain subgroups of patients, such as those with a higher age or with a history of chronic hypertension. A comparison of different strategies of targeting tissue perfusion rather than single value MAP targets may be more informative.

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Footnote

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