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Is There a Good MAP for Septic Shock?
James A. Russell, M.D.

As fundamental as the issue is, there is no clear, high-level evidence to determine the most effective mean arterial pressure (MAP) for resuscitation of patients with septic shock. During hypotension, three salient aspects of cardiovascular physiology are important. First, the autoregulation of cerebral blood flow maintains an adequate level over a wide range of pressures until a critical pressure (about 50 mm Hg) is reached; below this level, as the pressure falls, so does cerebral blood flow. Second, chronic hypertension shifts the autoregulatory curve of the relationship between pressure and perfusion so that perfusion is decreased at a higher critical pressure; long-term antihypertensive treatment restores the autoregulatory curves toward normal. Third, there are differences among organs in the critical point for oxygen delivery: gut oxygen delivery decreases earlier in shock than oxygen delivery to other organs. The consequence of inadequate perfusion is ischemic injury to the kidney, gut, brain, and myocardium, followed by multiple organ dysfunction and death.

The goal of cardiovascular resuscitation of septic shock is to improve organ perfusion, often by increasing the MAP. Adequate fluid resuscitation is limited when the administration of fluids causes edema (e.g., acute lung injury). Vasopressors are added if fluid resuscitation does not restore adequate perfusion, but such therapy is limited by excessive vasoconstriction and organ ischemia. A common clinical problem is distinguishing between ischemia that is caused by inadequate resuscitation (e.g., as manifested by oliguria) and ischemia that is caused by excessive vasoconstriction.

Reviews and sepsis guidelines recommend a target MAP of more than 65 mm Hg in patients with septic shock. However, these recommendations are based on low-quality evidence. Accordingly, Asfar et al. now report in the Journal the results of a large, randomized, controlled trial of targeting a low MAP (65 to 70 mm Hg) versus a high MAP (80 to 85 mm Hg) among patients with septic shock at 29 centers in France. By 28 days, there was no significant difference in mortality (the primary end point) between the low-target group and the high-target group. In the prospectively defined stratum of patients with chronic hypertension (more than 40% of the patients), those in the high-target group had less renal dysfunction and need for renal-replacement therapy than did those in the low-target group. However, there was a safety concern, since patients in the high-target group had an increased risk of new atrial fibrillation, which is
independently associated with an increased risk of stroke.\textsuperscript{5} Unfortunately, stroke was not evaluated by Asfar and colleagues.

The strengths of this trial are that the intervention was assigned by blinded randomization in a multicenter context in intensive care units; the two study groups were well balanced; the intervention was a pragmatic, real-world study; and the difference in ranges of MAP values between the two groups was significant. One limitation was that the interventions targeting a low or high MAP were not blinded.

How do these results align with those of other randomized, controlled trials of vasoactive interventions in shock? I compared intervention application and outcomes of this study with both published and unpublished data regarding the norepinephrine control groups of large, randomized, controlled trials of shock\textsuperscript{6-10} (Table 1). As compared with the findings in the study by Asfar et al., the target and actual MAP on day 1 in trials in which vasoactive agents were used were similar to those in the low-target group and lower than those in the high-target group. Asfar and colleagues used less fluid and higher doses of norepinephrine than were used in some trials\textsuperscript{8-10} but administered less norepinephrine and lower fluid levels than were used in another trial.\textsuperscript{7} Thus, there is variability in how fluids and vaso-pressors are used to achieve target MAPs in randomized, controlled trials. Finally, rates of death in the trial by Asfar et al. were similar to those in two trials,\textsuperscript{6,10} higher than those in one trial,\textsuperscript{8} and lower than those in two other trials.\textsuperscript{7,9} These mortality differences may arise from differences in the inclusion criteria used in these trials (septic shock,\textsuperscript{4,6,10} severe sepsis,\textsuperscript{9} and shock\textsuperscript{7,8}) and trial location,\textsuperscript{4,6-10} since mortality associated with

### Table 1. Comparison of Norepinephrine Control Groups and Intervention Groups in Randomized, Controlled Trials of Vasoactive Agents in Shock.\textsuperscript{*}

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean Arterial Pressure (MAP)</th>
<th>Norepinephrine Infusion Rate</th>
<th>Fluid Balance</th>
<th>Renal-Replacement Therapy</th>
<th>Death at 28 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target</td>
<td>Actual, Day 0</td>
<td>Actual, Day 1</td>
<td>Day 0</td>
<td>Day 1</td>
</tr>
<tr>
<td>Asfar et al.\textsuperscript{,}††</td>
<td>65 to 70</td>
<td>74</td>
<td>74</td>
<td>0.35</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Low-target group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td>65 to 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with chronic hypertension</td>
<td>65 to 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-target group</td>
<td>80 to 85</td>
<td>74</td>
<td>84</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td>80 to 85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with chronic hypertension</td>
<td>80 to 85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annane et al.\textsuperscript{,}‡</td>
<td>70</td>
<td>70</td>
<td>80</td>
<td>0.94</td>
<td>1.09</td>
</tr>
<tr>
<td>De Backer et al.\textsuperscript{,}7</td>
<td>MD</td>
<td>58</td>
<td>76</td>
<td>0.54</td>
<td>0.82</td>
</tr>
<tr>
<td>Myburgh et al.\textsuperscript{,}¶</td>
<td>MD</td>
<td>70</td>
<td>73</td>
<td>0.26</td>
<td>0.17</td>
</tr>
<tr>
<td>Rivers et al.\textsuperscript{,}‖</td>
<td>65</td>
<td>76</td>
<td>81</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Russell et al.\textsuperscript{,}10</td>
<td>65 to 75</td>
<td>72</td>
<td>73</td>
<td>0.28</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\textsuperscript{*} MD indicates clinician judgment, and NA not available.  
\textsuperscript{†} Listed are results for both the control (low-target) group and the intervention (high-target) group.  
\textsuperscript{‡} In the study by Annane et al., fluid balance was reported for survivors only.  
\textsuperscript{¶} The percentage was 19.9\% in the subgroup with septic shock.  
\textsuperscript{‖} In the study by Rivers et al., if no target MAP was ordered, the default target MAP was 70 mm Hg.  
\textsuperscript{**} Fluid balance was averaged over 3 days rather than 4.
septic shock varies according to country,\textsuperscript{11} making comparisons between countries and continents difficult.

The findings of Asfar et al. have at least three major clinical implications. First, they show that there is no indication for routinely targeting a high MAP in patients with septic shock, since there was no significant between-group difference in mortality, although patients in the high-target group had an increased rate of atrial fibrillation. Second, a high MAP target may decrease the risk of renal injury and the need for renal-replacement therapy (number needed to treat of 9.5 to prevent one patient from needing renal-replacement therapy) in patients with hypertension. I make this point because of the well-known risks and costs of renal-replacement therapy. Thus, there are several target MAPs for septic shock, depending on the circumstances of the patient. In some randomized, controlled trials (and in clinical practice), practitioners use more fluid (increasing the risk of acute lung injury), whereas others use more vasopressors (increasing the risk of renal injury). Indeed, methods for targeting a MAP among patients in septic shock are probably critical to the success of the strategy and deserving of greater investigation.

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