F1000 FACULTY CRITIQUE

Where is the vascular waterfall in septic shock? [version 1; referees: not peer reviewed]

Ryotaro Kato[1], Michael Pinsky[1,2]

[1]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA
[2]The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, University of Pittsburgh, Pittsburgh, PA, USA

v1 **First published:** 19 Nov 2015, **4**:1294 (doi: 10.12688/f1000research.6820.1)
Latest published: 19 Nov 2015, **4**:1294 (doi: 10.12688/f1000research.6820.1)

Abstract

An evaluation of a recent study by Asfar P, Meziani F, Hamel J-F, *et al*. **High versus low blood-pressure target in patients with septic shock**. N Engl J Med 2014;370:1583-1593.

This article is included in the Critical care channel.

Not Peer Reviewed

This article is an F1000 Faculty Critique and has not been subject to external peer review.

Discuss this article

Comments (0)

Corresponding author: Michael Pinsky (pinskymr@upmc.edu)

How to cite this article: Kato R and Pinsky M. **Where is the vascular waterfall in septic shock? [version 1; referees: not peer reviewed]** *F1000Research* 2015, **4**:1294 (doi: 10.12688/f1000research.6820.1)

Copyright: © 2015 Kato R and Pinsky M. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Competing interests: The authors declare that they have no competing interests.

First published: 19 Nov 2015, **4**:1294 (doi: 10.12688/f1000research.6820.1)

Critique of:

Citation

Asfar P, Meziani F, Hamel J-F, *et al.* High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370: 1583–1593.

Background

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mmHg during initial resuscitation of patients with septic shock. However, whether this blood pressure target is more or less effective than a higher target is unknown.

Methods

Objective

To determine whether targeting a mean arterial pressure of 80 to 85 mmHg would decrease 28-day mortality, as compared with targeting a mean arterial pressure of 65 to 70 mmHg. The sub-hypothesis of the study was that the beneficial effects of a higher target would be more pronounced among patients with chronic hypertension.

Design

The Assessment of Two Levels of Arterial Pressure on Survival in Patients with Septic Shock (SEPSISPAM) is a multi-center, randomized, stratified, open-label, prospective trial involving patients with septic shock. The patients were stratified according to whether they had a history of chronic hypertension. The data analysis was conducted on an intention-to-treat basis.

Setting

Intensive care units in 29 centers in France from March 2010 through December 2011.

Subjects

Patients older than 18 years of age who had septic shock refractory to fluid resuscitation, required vasopressors at a minimum infusion rate of 0.1 mcg/kg/min and evaluated within 6 hours after the initiation of vasopressors. Subjects were excluded if they had legal protection, had no affiliation with French health care system, were pregnant, recently participated in another biochemical study or another interventional study with mortality as the primary endpoint, or were decided by the investigators not to resuscitate.

Intervention

After their enrollment, subjects were assigned to maintain a mean arterial pressure of 80 to 85 mmHg (high-target group) or 65 to 70 mmHg (low-target group) using protocolized hemodynamic management strategies that employed norepinephrine as the first line vasopressor. Target mean arterial pressure was maintained for maximum of 5 days or until the subjects were weaned off from vasopressor support.

Outcomes

The primary outcome was death from any cause by 28 days after inclusion. Secondary outcomes were 90-day mortality, days alive and free from organ dysfunction by day 28, and the length of stay in the intensive care unit (ICU) and hospital.

Results

At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; P = 0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; P = 0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; P = 0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

Conclusion

Targeting a mean arterial pressure of 80 to 85 mmHg, as compared with 65 to 70 mmHg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days.

Abstract adapted from the original provided courtesy of PubMed: A service of the National Library of Medicine and the National Institutes of Health.

Commentary

For the patients suffering from septic shock who remain hypotensive despite of adequate fluid resuscitation, the guidelines of the Surviving Sepsis Campaign 2012 recommended initial resuscitation with vasopressors to maintain a mean arterial pressure (MAP) of at least 65 mmHg. For the patients with atherosclerosis or previous hypertension, however, the Surviving Sepsis Campaign guidelines cautioned that maintaining a higher MAP might be better[1].

These recommendations were based on limited, sometimes conflicting results from small studies, the committee members' personal practice and traditional pressure thresholds used in prior clinical trials of sepsis resuscitation that did not study target blood pressure levels. Some of these studies revealed that MAP under 65 mmHg was associated with highest mortality in patients with septic shock[2], but targeting a MAP higher than 65 mmHg conferred no additional benefit[3,4]. Looking specifically at renal function, however, other studies found that targeting a higher MAP was beneficial[5–7]. In reality, the majority of critical care practitioners seem to be targeting a MAP higher than 65 mmHg[8]. Clearly, more studies are warranted to determine the optimal MAP target in patients with septic shock.

In this context, the Assessment of Two Levels of Arterial Pressure on Survival in Patients with Septic Shock (SEPSISPAM) was conducted at 29 centers in France from March 2010 through December 2011, to determine whether targeting a MAP of 65 to 70 mmHg was more or less effective than targeting a higher MAP.

The hypothesis of this study was based on a sound physiological rationale. Human bodies, like in other mammals, require relatively high blood pressure to allow autoregulation of blood flow distribution. Autoregulation is the intrinsic ability of our organs to maintain a constant blood flow despite changes in perfusion pressure. It operates by changes in local vasomotor tones, but it has its limits. If the perfusion pressure falls below a threshold point where the blood vessels are already maximally dilated, autoregulation-induced local vasodilation will no longer sustain constant organ blood flow. At these lower blood pressure limits, organ blood flow usually decreases proportionally to the decline in perfusion pressure and below the flow needed to support basal metabolism. Ultimately, when the perfusion pressure reaches the critical closing pressure or outflow pressure, organ flow ceases completely. Hence, it is important for critical care practitioners to know their patients' threshold pressure of autoregulation, if they wish their resuscitation targets to result in organ perfusion and sustained tissue viability.

Under normal conditions, arteriolar tone will cause vessels to collapse and stop arterial flow once the intraluminal pressure is less than the intrinsic arteriolar wall vasomotor tone. This pressure is referred to as the vessel's critical closing pressure or outflow pressure. Critical closing pressure can be estimated by describing the relationship between input arterial pressure (P) and organ blood flow (Q) over a range of pressures and flows[9]. Plotting P on x-axis and Q on y-axis, the slope Q/P represents Ohmic resistance of the vessels. Increase in Ohmic resistance leads to increase in perfusion pressure necessary to maintain steady organ flow. A caveat here is that the blood flow ceases at a pressure much higher than zero. For most vascular circuits, the Q/P relationship decays to an extrapolated pressure at zero flow (Pzf) which reflects this critical closing pressure. The critical closing pressure is a function of arteriolar and pre-capillary sphincter tone and varies amongst vascular beds, dependent upon overall sympathetic tone and local metabolic demands. As a lumped sum parameter, it is thought to be around 45 mmHg in normal health adults at rest and remains higher than the mean systemic filling pressure, even in vasoplegic states. This difference between the local critical closing pressure and mean systemic filling pressure signifies the existence of a vascular waterfall in the arterial circuit[10]. With increasing hypotension and its associated local vasodilation in metabolically active tissues, some minimal pressure gradient is ultimately reached, below which flow will decrease if arterial input pressure decreases further.

Although the actual organ perfusion pressure is unknown in most cases, the discussion is not academic, but highly clinical, because it is the organ perfusion pressure that defines whether a given MAP is above or below the threshold value that allows autoregulation to occur.

Importantly, autoregulation is organ specific[11] and can be altered by disease processes, including hypertension and sepsis[12]. Hence, the sub-hypothesis of the SEPSISPAM study was that the beneficial effects of a higher target MAP would be more pronounced among patients with chronic hypertension.

The SEPSISPAM study was well designed. It was a multi-center, randomized, stratified, open-label, prospective trial involving patients with septic shock. The investigators screened 4,098 patients for eligibility, but 3,298 of them were considered not eligible, primarily because they did not meet the inclusion criteria. Of 1,682 patients who did not meet the inclusion criteria, 858 had shock lasting more than 6 hours. Whether or not exclusion of this many patients may have impacted the pragmatic nature of study is unknown.

Impressively, the investigators were able to recruit and randomize 798 patients out of 800 eligible patients. Eventually, 776 patients were included in 90-day follow-up and analysis. Baseline characteristics of the two groups were very similar. 167 patients (43%) in the high-target group and 173 patients (44.6%) in the low-target group had a history of chronic hypertension.

Due to the nature of its intervention, it was necessarily open-label. Still, this might have had significant impact on the results. Majority of the patients assigned to the high-target group achieved a MAP of 85 to 90 mmHg, while majority of the patients assigned to the low-target group achieved a MAP of 70 to 75 mmHg. Even though the study was able to maintain the difference in MAP between the two groups, the inflation in the low-target group's MAP values precluded answers to the question regarding the lowest threshold MAP required to preserve the organ blood flow.

This study allowed targeting a MAP using protocolized hemodynamic management strategies using fluid resuscitation and vasopressors alone. Reportedly, intravenous fluids were administered at clinicians' discretion based on hemodynamic variables such as right heart catheterization, pulse pressure and stroke volume measurement or echocardiography, which were also part of the study's inclusion criteria, but those data were not reported. Overall fluid resuscitation in both study groups was lower than in previously reported studies, suggesting that fluid resuscitation was less vigorous than traditionally performed.

The study showed that there was no significant between-group difference in the rate of death at 28 days and at 90 days. For the patients with chronic hypertension, the low-target group had a higher incidence of the doubling of creatinine level and the need for renal replacement therapy. This finding confirms that the optimal MAP differs not only between individual patients, but also between individual organs, with those patients with chronic hypertension requiring a higher MAP to prevent renal injury. There is no "one-size fits all" when it comes to optimal MAP for a patient with septic shock. Critical care practitioners must be able to adjust the target MAP based on their patients' clinical responses, such as urine output or serum lactate level. This approach may be difficult when it comes to the assessment of cerebral blood flow, as there are no reliable clinical indicators. Outcomes on neurocognitive functions were not reported in this study, but they are anticipated to be part of the upcoming sub-study report[13].

Importantly, targeting a higher MAP in all patients, including those without hypertension, was also not without risk. Although this study was underpowered to detect any differences in incidence of most of the adverse events, which were rare, the majority of adverse events were reported higher in the high-target group. These findings are not surprising because the infusion rates and the duration of vasopressors

were higher in the high-target group. The incidence of newly diagnosed atrial fibrillation was significantly higher in the high-target group, with events reported in 26 patients (6.7%) in the high-target group and 11 patients (2.8%) in the low-target group. New onset atrial fibrillation may be associated with increased incidence of in-hospital stroke and death[14]. The investigators limited the types of vasopressor used with norepinephrine as the primary choice. If vasopressin had been used, which is known to be associated with less tachyarrhythmia, the adverse event profile might have looked different[15].

Finally, the generalizability of the study may have been limited because of the frequent use of corticosteroids and occasional use of activated protein C, which do not represent present-day standard of care. Corticosteroids were used in 327 patients (85%) in the high-target group and 307 patients (80%) in the low-target group. Activated protein C was used in 29 patients (7.5%) in the high-target group and 26 patients (6.8%) in the low-target group.

Still, these data reflect the largest and best-controlled study of targeted blood pressure in septic shock published to date. They support the conclusion that targeting a MAP of 65 to 70 mmHg in a patient without prior chronic hypertension is a reasonable first approximation, after which time MAP levels can be adjusted up or down as end organ function dictates. Whereas in the patient with chronic hypertension, a higher baseline MAP around 80 to 85 mmHg is appropriate with similar post target changes made as end-organ perfusion defines.

Recommendation

The findings of this study underscore the importance of personalized medicine during resuscitation from septic shock. While targeting a MAP of 65 to 70 mmHg is a reasonable first step, critical care practitioners must be able to adjust the target MAP based on their patients' subsequent clinical response. Targeting a higher MAP around 80 to 85 mmHg appears to be a reasonable first step for a patient with chronic hypertension, but it should be done with caution because higher doses and duration of vasopressors will be necessary and will carry increase risk of cardiovascular complications.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. Dellinger RP, Levy MM, Rhodes A, *et al.*: **Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.** *Crit Care Med.* 2013; **41**(2): 580–637.
PubMed Abstract | Publisher Full Text
2. Varpula M, Tallgren M, Saukkonen K, *et al.*: **Hemodynamic variables related to outcome in septic shock.** *Intensive Care Med.* 2005; **31**(8): 1066–71.
PubMed Abstract | Publisher Full Text
3. LeDoux D, Astiz ME, Carpati CM, *et al.*: **Effects of perfusion pressure on tissue perfusion in septic shock.** *Crit Care Med.* 2000; **28**(8): 2729–32.
PubMed Abstract
4. Bourgoin A, Leone M, Delmas A, *et al.*: **Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function.** *Crit Care Med.* 2005; **33**(4): 780–6.
PubMed Abstract
5. Dünser MW, Takala J, Ulmer H, *et al.*: **Arterial blood pressure during early sepsis and outcome.** *Intensive Care Med.* 2009; **35**(7): 1225–33.
PubMed Abstract | Publisher Full Text
6. Badin J, Boulain T, Ehrmann S, *et al.*: **Relation between mean arterial pressure and renal function in the early phase of shock: a prospective, explorative cohort study.** *Crit Care.* 2011; **15**(3): R135.
PubMed Abstract | Publisher Full Text | Free Full Text
7. Poukkanen M, Wilkman E, Vaara ST, *et al.*: **Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study.** *Crit Care.* 2013; **17**(6): R295.
PubMed Abstract | Publisher Full Text | Free Full Text
8. Russell JA: **Is there a good MAP for septic shock?** *N Engl J Med.* 2014; **370**(17): 1649–51.
PubMed Abstract | Publisher Full Text
9. Bellomo R, Kellum JA, Wisniewski SR, *et al.*: **Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs.** *Am J Respir Crit Care Med.* 1999; **159**(4 Pt 1): 1186–92.
PubMed Abstract | Publisher Full Text
10. Maas JJ, de Wilde RB, Aarts LP, *et al.*: **Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the intensive care unit.** *Anesth Analg.* 2012; **114**(4): 803–10.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Kramer DJ, Stein K, Schlichtig R, *et al.*: **Pressure flow relationship in the superior mesenteric and hepatic arteries in endotoxic shock.** *Chest.* 1989; **96**: 293S.
12. Di Giantomasso D, May CN, Bellomo R: **Vital organ blood flow during hyperdynamic sepsis.** *Chest.* 2003; **124**(3): 1053–9.
PubMed Abstract | Publisher Full Text
13. Asfar P, Teboul JL, Radermarcher P: **High versus low blood-pressure target in septic shock.** *N Engl J Med.* 2014; **371**(3): 282–4.
PubMed Abstract | Publisher Full Text
14. Walkey AJ, Wiener RS, Ghobrial JM, *et al.*: **Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis.** *JAMA.* 2011; **306**(20): 2248–54.
PubMed Abstract | Publisher Full Text | Free Full Text
15. Dünser MW, Mayr AJ, Ulmer H, *et al.*: **Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study.** *Circulation.* 2003; **107**(18): 2313–9.
PubMed Abstract | Publisher Full Text