STANDARD LOWER MAP GOAL IN PATIENTS WITH SEPTIC SHOCK

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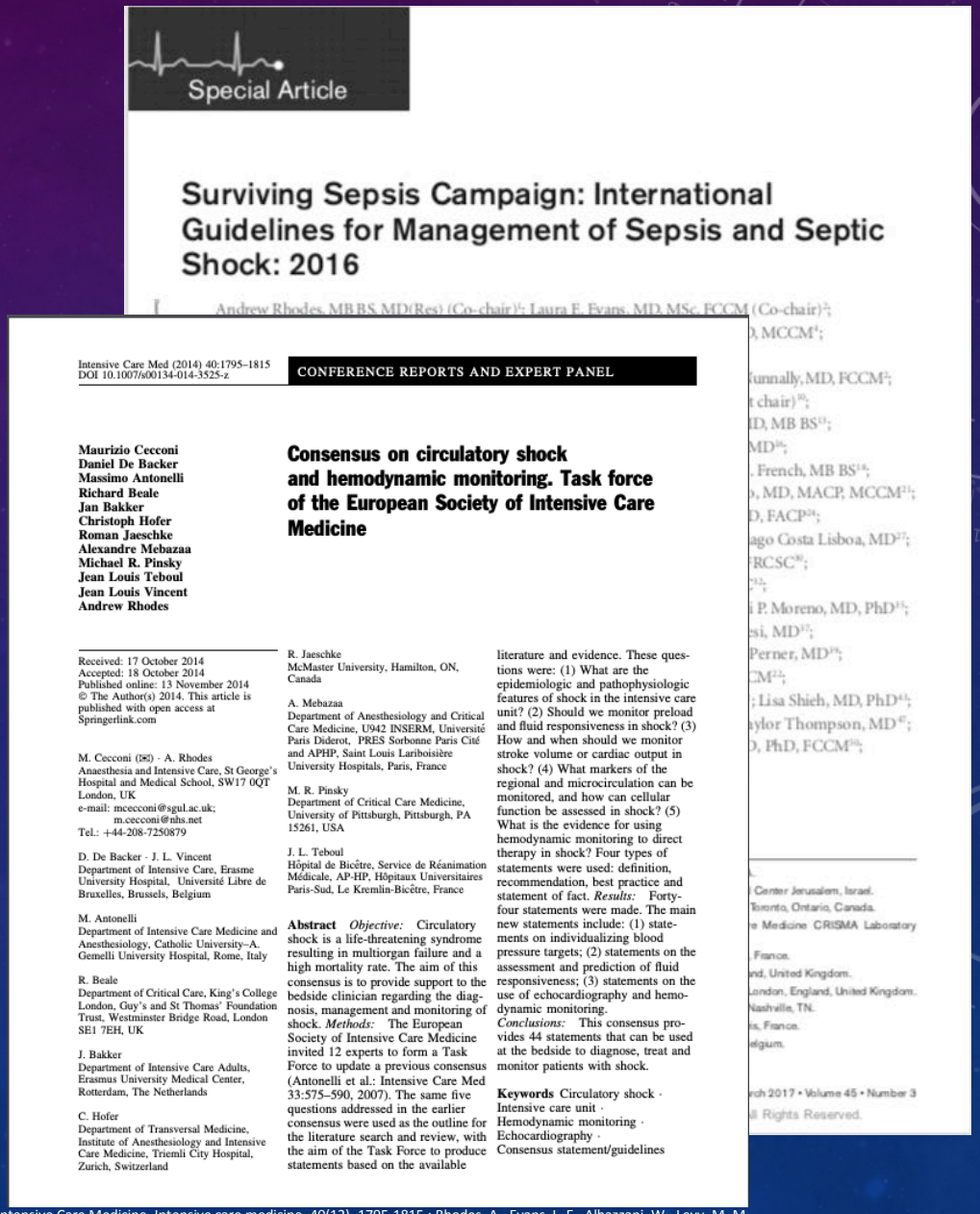
OBJECTIVES

- Identify patient populations that may benefit from a lower MAP goal during septic shock
- Explain risks associated with targeting a lower MAP goal during septic shock

SEPSIS GUIDELINES

- We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
- We recommend to initially target a MAP of ≥65 mmHg. *Recommendation*. Level 1; QoE low (C).



Special Article

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

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Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

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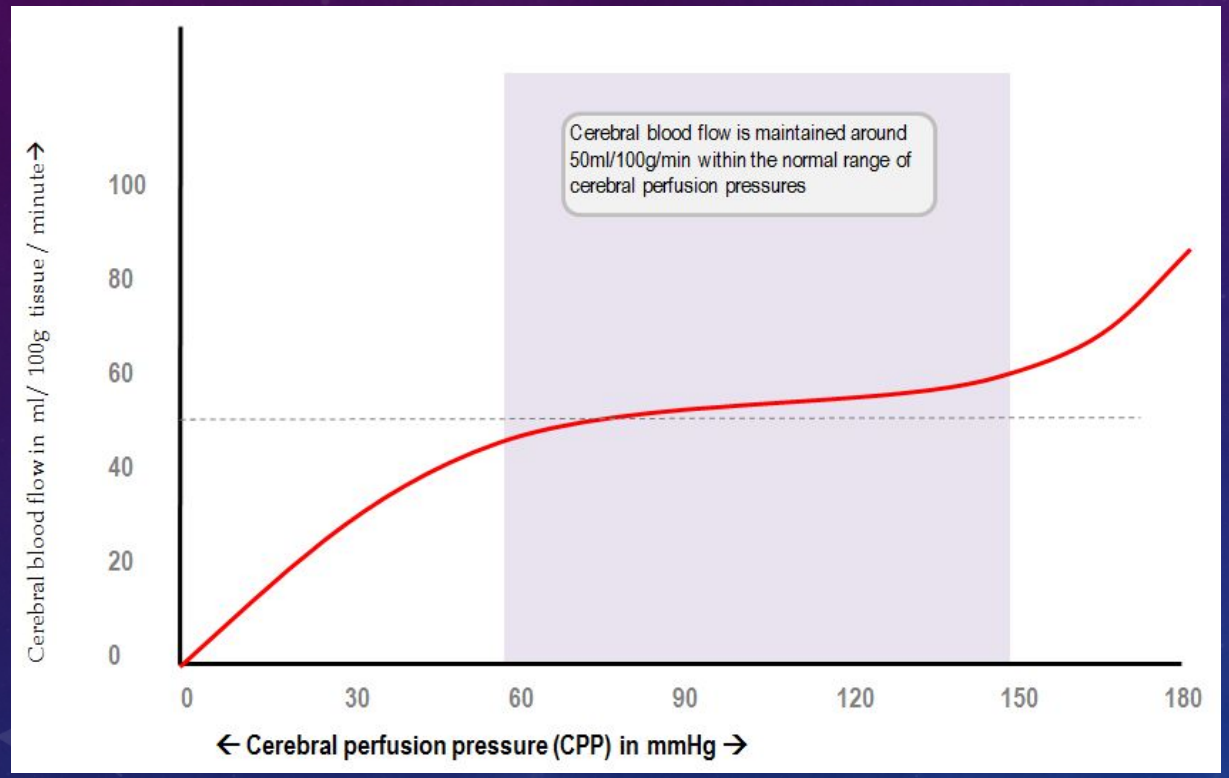
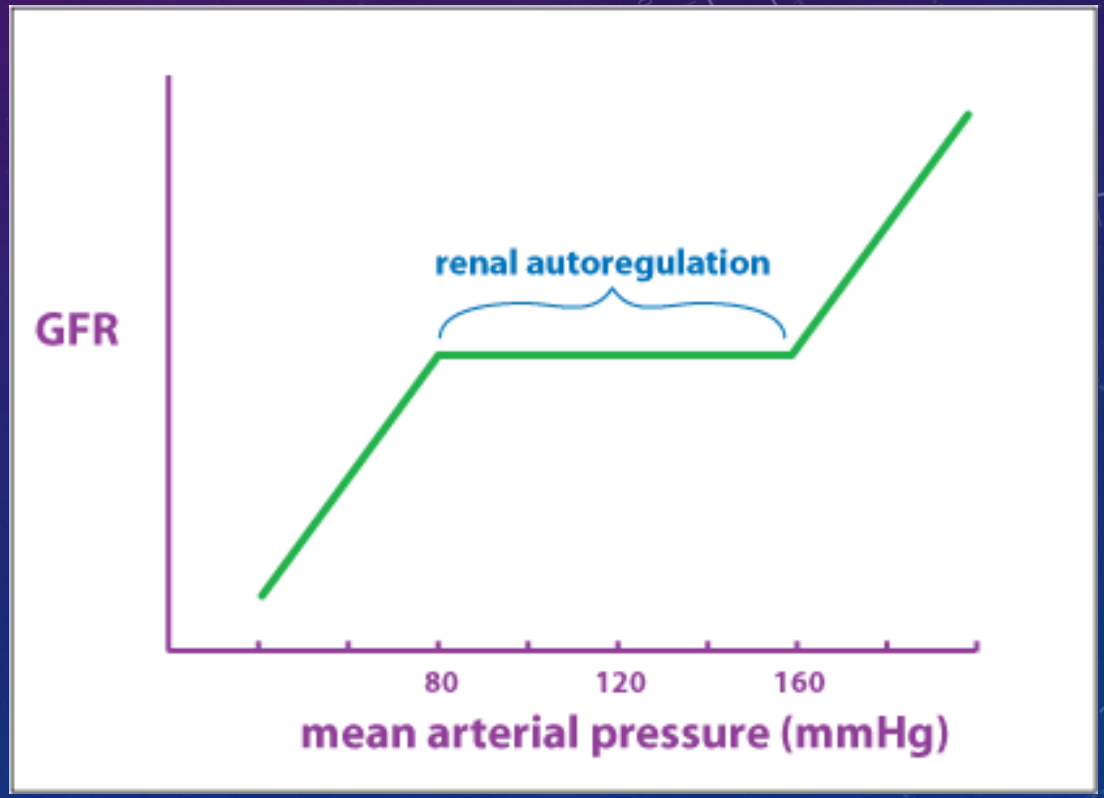
Abstract *Objective:* Circulatory shock is a life-threatening syndrome resulting in multiorgan failure and a high mortality rate. The aim of this consensus is to provide support to the bedside clinician regarding the diagnosis, management and monitoring of shock. *Methods:* The European Society of Intensive Care Medicine invited 12 experts to form a Task Force to update a previous consensus (Antonelli et al.: Intensive Care Med 33:575–590, 2007). The same five questions addressed in the earlier consensus were used as the outline for the literature search and review, with the aim of the Task Force to produce statements based on the available literature and evidence. These questions were: (1) What are the epidemiologic and pathophysiologic features of shock in the intensive care unit? (2) Should we monitor preload and fluid responsiveness in shock? (3) How and when should we monitor stroke volume or cardiac output in shock? (4) What markers of the regional and microcirculation can be monitored, and how can cellular function be assessed in shock? (5) What is the evidence for using hemodynamic monitoring to direct therapy in shock? Four types of statements were used: definition, recommendation, best practice and statement of fact. *Results:* Forty-four statements were made. The main new statements include: (1) statements on individualizing blood pressure targets; (2) statements on the assessment and prediction of fluid responsiveness; (3) statements on the use of echocardiography and hemodynamic monitoring. *Conclusions:* This consensus provides 44 statements that can be used at the bedside to diagnose, treat and monitor patients with shock.

Keywords Circulatory shock · Intensive care unit · Hemodynamic monitoring · Echocardiography · Consensus statement/guidelines

Cecconi, M., De Backer, D., Antonelli, M., Beale, R., Bakker, J., Hofer, C., ... & Vincent, J. L. (2014). Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive care medicine, 40(12), 1795-1815.; Rhodes, A., Evans, L. E., Alhazzani, W., Levy, M. M., Antonelli, M., Ferrer, R., ... & Rochwerg, B. (2017). Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive care medicine, 43(3), 304-377.

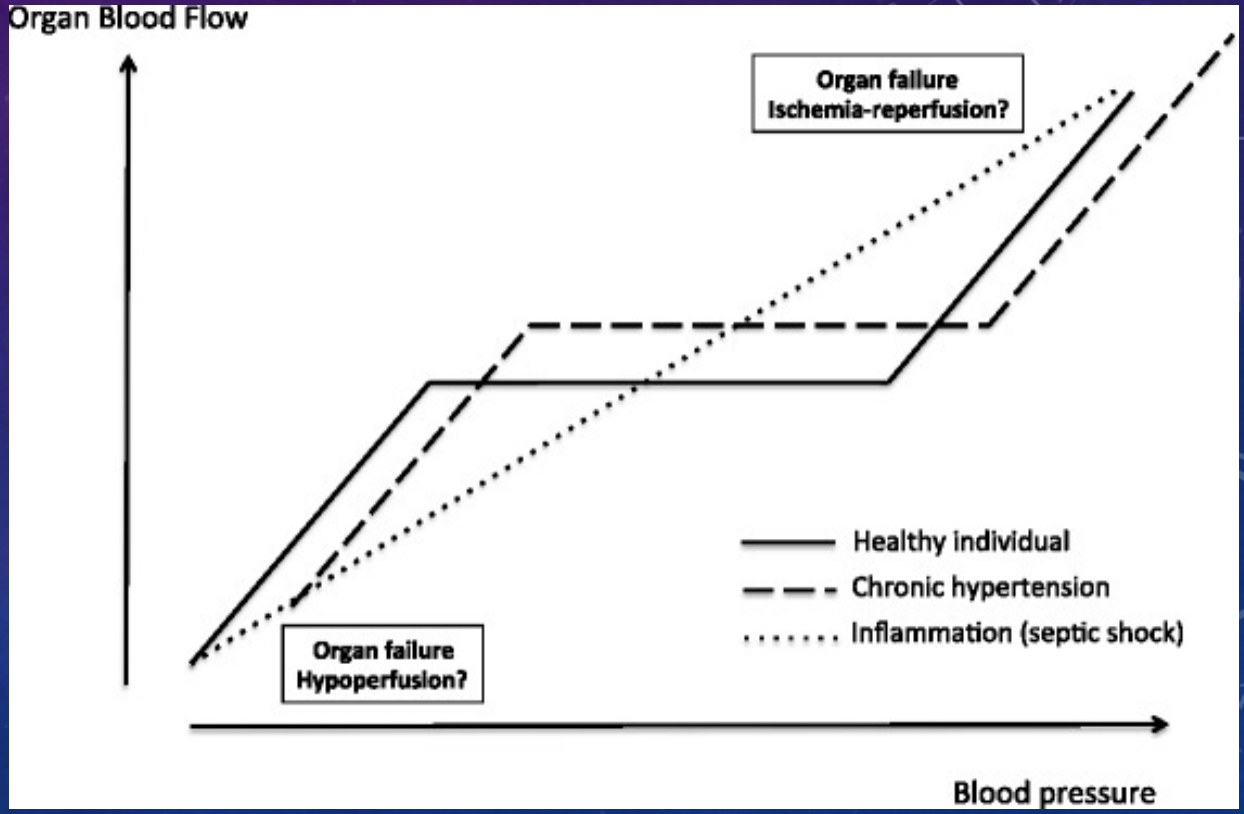
AUTOREGULATION





OPTIMAL MAP GOAL

- MAP target that is too low may be associated with organ hypoperfusion
- MAP target that is too high may be associated with ischemic injury due to excessive vasoconstriction.



Leone, M., Asfar, P., Radermacher, P., Vincent, J. L., & Martin, C. (2015). Optimizing mean arterial pressure in septic shock: a critical reappraisal of the literature. Critical Care, 19(1), 101.

SEPSISPAM TRIAL

- Multicenter, randomized, open label, controlled trial
- N=776
  - MAP goal 65-70 mmHg (n=388)
  - MAP goal 80-85 mmHg (n=388)
- Setting: 29 French centers
- Enrollment: 2010-2011
- Follow-up: 90 days
- Analysis: Intention-to-treat
- Primary outcomes: All-cause mortality at day 28

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High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D., for the SEPSISPAM Investigators*

ABSTRACT

BACKGROUND

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg 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

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

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.

CONCLUSIONS

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Asfar at the Department of Medical Intensive Care and Hyperbaric Medicine, University Hospital of Angers, 4 rue Larrey, F-49933 Angers CEDEX 9, France, or at piasfar@chu-angers.fr.

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SEPSISPAM TRIAL

- For patients with septic shock, a goal MAP of 80-85 mmHg does not reduce all-cause mortality at 28 days (or 90 days) when compared to a goal of 65-70 mmHg.
- The higher MAP goal was associated with reduction in rates of renal dysfunction (and RRT) for patients with a history of chronic hypertension.
- High MAP targets are associated with adverse effects from the catecholamine infusions.

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SEPSISPAM TRIAL

- The infusion rates of vasopressors were significantly higher
- Duration of vasopressor treatment significantly longer, in the high-target group than in the low-target group
- The optimal blood pressure target likely ranges from 65 to 85 mm Hg and PROBABLY lies between 65 and 75 mm Hg in most patients

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MAP TARGET ABNORMALITIES

- MAPs in the low-target group (65 to 70 mm Hg) were for the most part ACTUALLY between 70 and 75 mm Hg.

- Values in the high-target group (80 to 85 mm Hg) were also ACTUALLY higher ranging between 85 and 90 mm Hg

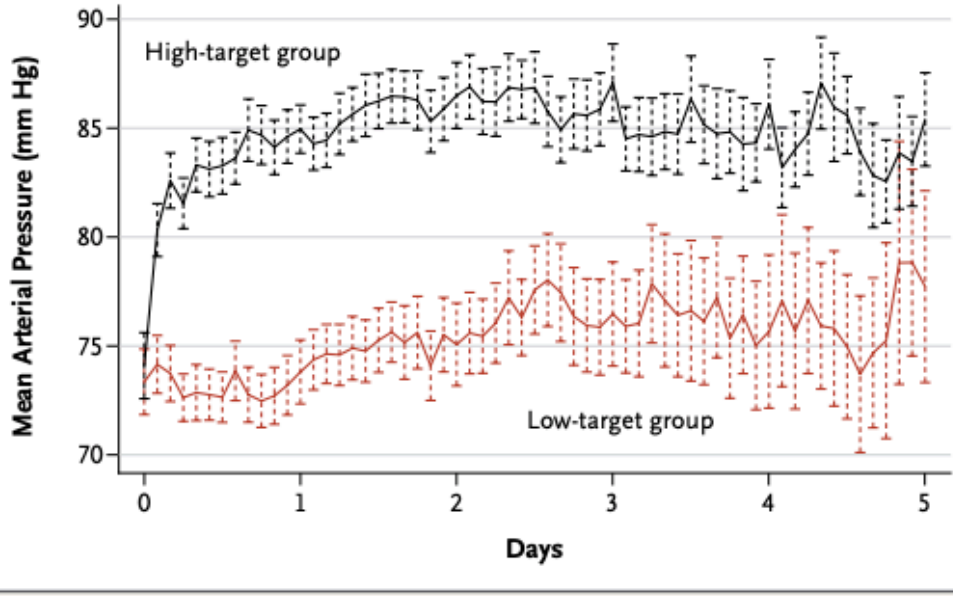

Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

Mean arterial pressures were significantly lower in the low-target group than in the high-target group during the 5 protocol-specified days (P=0.02 by repeated-measures regression analysis), although the values exceeded the target values of 80 to 85 mm Hg in the high-target group and 65 to 70 mm Hg in the low-target group. The I bars represent 95% confidence intervals.

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MAP TARGET ABNORMALITIES

- Poukkanen et al., found that patients spent more than 75% of the time at a mean arterial pressure of more than 70 mmHg
- Leone and colleagues found that a MAP goal was pre-fixed in only 70% of patients with septic shock.
  - MAP ≥ 65 mmHg
- Lamontagne et al., noted MAP was frequently above the prescribed range.
- Role of monitor alarms

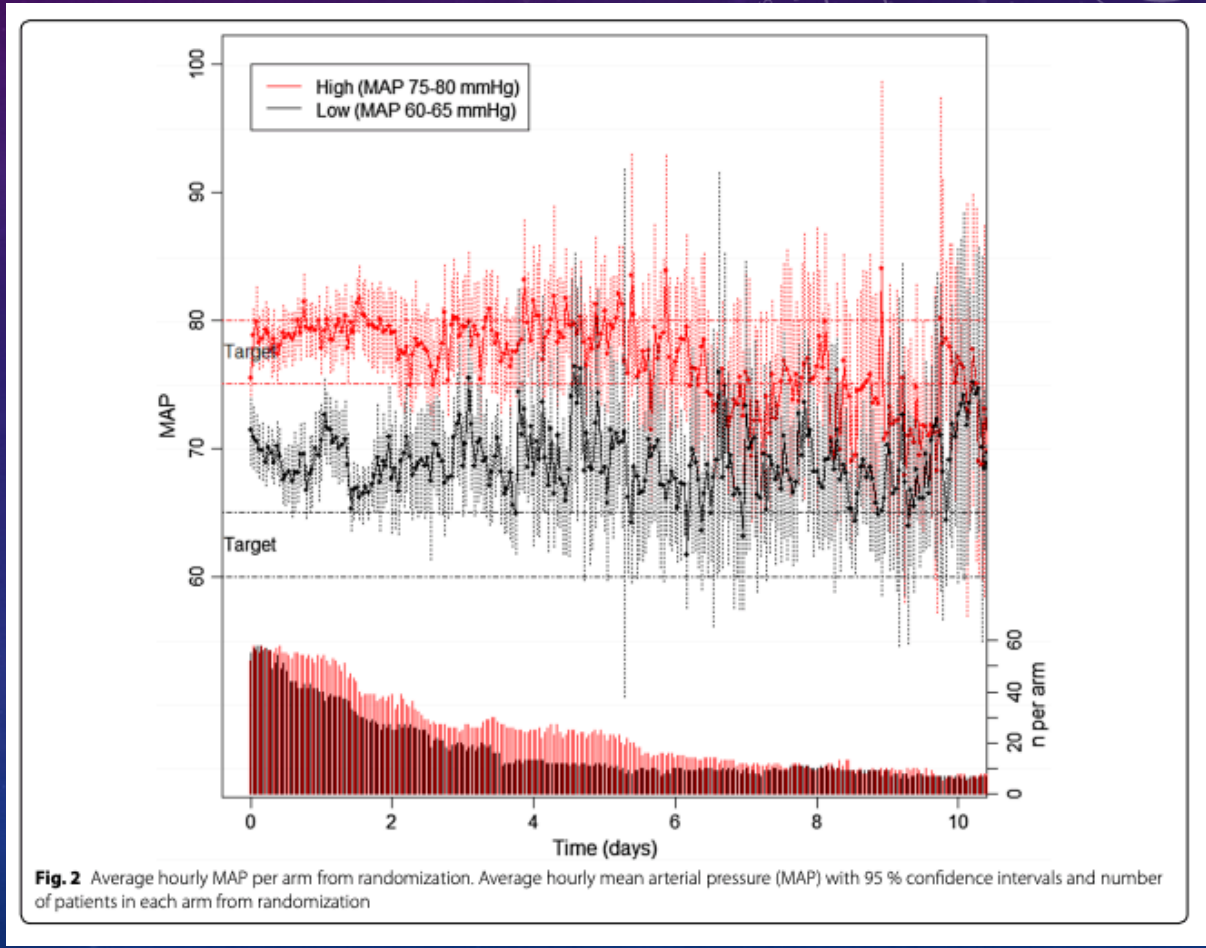
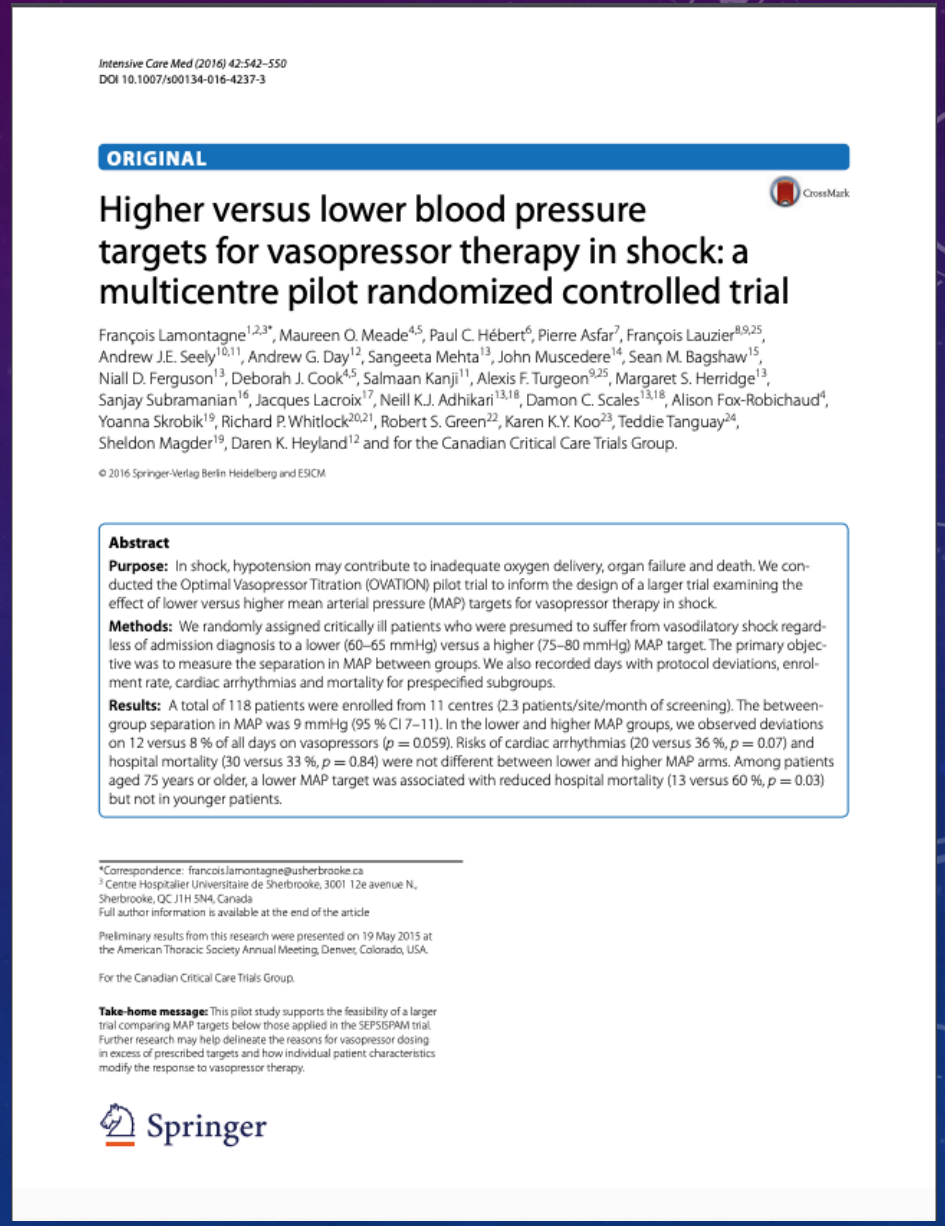


Fig. 2 Average hourly MAP per arm from randomization. Average hourly mean arterial pressure (MAP) with 95 % confidence intervals and number of patients in each arm from randomization

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:R295. Leone M, Ragonnet B, Alonso S, Allaouchiche B, Constantin JM, Jaber S, Martin C, Fabbro-Peray P, Lefrant JY, AzuRéa Group Variable compliance with clinical practice guidelines identified in a 1-day audit at 66 French adult intensive care units. Crit Care Med. 2012;40:3189–95. Lamontagne, F., Meade, M. O., Hébert, P. C., Asfar, P., Lauzier, F., Seely, A. J., ... & Ferguson, N. D. (2016). Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive care medicine, 42(4), 542-550.

OVATION PILOT TRIAL

- 118 patients were enrolled from 11 centers in Canada
- Risks of cardiac arrhythmias and hospital mortality were not different between lower and higher MAP arms.
- Among patients aged 75 years or older, a lower MAP target was associated with reduced hospital mortality (13 versus 60 %, p = 0.03) but not in younger patients.
- Nurses and physicians take great care to avoid under-dosing vasopressors, but may under-appreciate or under-value the potential risks of excessive vasopressor therapy in excess of prescribed



Intensive Care Med (2016) 42:542–550
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ORIGINAL

Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial

François Lamontagne[1,2,3*], Maureen O. Meade[4,5], Paul C. Hébert[6], Pierre Asfar[7], François Lauzier[8,9,25], Andrew J.E. Seely[10,11], Andrew G. Day[12], Sangeeta Mehta[13], John Muscedere[14], Sean M. Bagshaw[15], Niall D. Ferguson[13], Deborah J. Cook[4,5], Salmaan Kanji[11], Alexis F. Turgeon[9,25], Margaret S. Herridge[13], Sanjay Subramanian[16], Jacques Lacroix[17], Neill K.J. Adhikari[13,18], Damon C. Scales[13,18], Alison Fox-Robichaud[4], Yoanna Skrobik[19], Richard P. Whitlock[20,21], Robert S. Green[22], Karen K.Y. Koo[23], Teddie Tanguay[24], Sheldon Magder[19], Daren K. Heyland[12] and for the Canadian Critical Care Trials Group.

Abstract

Purpose: In shock, hypotension may contribute to inadequate oxygen delivery, organ failure and death. We conducted the Optimal Vasopressor Titration (OVATION) pilot trial to inform the design of a larger trial examining the effect of lower versus higher mean arterial pressure (MAP) targets for vasopressor therapy in shock.

Methods: We randomly assigned critically ill patients who were presumed to suffer from vasodilatory shock regardless of admission diagnosis to a lower (60–65 mmHg) versus a higher (75–80 mmHg) MAP target. The primary objective was to measure the separation in MAP between groups. We also recorded days with protocol deviations, enrolment rate, cardiac arrhythmias and mortality for prespecified subgroups.

Results: A total of 118 patients were enrolled from 11 centres (2.3 patients/site/month of screening). The between-group separation in MAP was 9 mmHg (95 % CI 7–11). In the lower and higher MAP groups, we observed deviations on 12 versus 8 % of all days on vasopressors ($p = 0.059$). Risks of cardiac arrhythmias (20 versus 36 %, $p = 0.07$) and hospital mortality (30 versus 33 %, $p = 0.84$) were not different between lower and higher MAP arms. Among patients aged 75 years or older, a lower MAP target was associated with reduced hospital mortality (13 versus 60 %, $p = 0.03$) but not in younger patients.

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Preliminary results from this research were presented on 19 May 2015 at the American Thoracic Society Annual Meeting, Denver, Colorado, USA.

For the Canadian Critical Care Trials Group.

Take-home message: This pilot study supports the feasibility of a larger trial comparing MAP targets below those applied in the SEPSISPAM trial. Further research may help delineate the reasons for vasopressor dosing in excess of prescribed targets and how individual patient characteristics modify the response to vasopressor therapy.

Springer

Lamontagne, F., Meade, M. O., Hébert, P. C., Asfar, P., Lauzier, F., Seely, A. J., ... & Ferguson, N. D. (2016). Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive care medicine, 42(4), 542-550.

TARGET POPULATION FOR LOWER MAP GOALS

- Per multiple guideline recommendations, all patients with septic shock should target MAP ≥65mmHg
- Populations where Lower MAP Goals have the highest recommendation:
  - Clinically-relevant bleeding
  - Major persistent arrhythmias
  - Myocardial infarction
  - Mesenteric ischemia
  - Distal-limb ischemia
  - ESRD patients
- Evolving literature in patients with TBI or delirium
  - Brain Trauma Foundation recommends a target CPP between 50 and 70 mmHg

Bratton, S. L., Chestnut, R. M., Ghajar, J., McConnell, F. H., Harris, O. A., Hartl, R., ... & Schouten, J. (2007). Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *Journal of neurotrauma*, *24*, S59-64. Kato, R., & Pinsky, M. R. (2015). Personalizing blood pressure management in septic shock. Annals of intensive care, 5(1), 41.

RISKS ASSOCIATED WITH LOWER MAP GOAL

- ORGAN HYPOPERFUSION
  - Brain
  - Kidneys
  - Heart
  - Liver
  - Splanchnic System

- Caution should be taken in ALL patients in using MAP alone as surrogate of organ perfusion pressure, especially under conditions in which intracranial or intra-abdominal pressure may be elevated.

- Titration methodologies should be optimized to decrease wide variations in MAP while the patient is receiving catecholamines.

Kato, R., & Pinsky, M. R. (2015). Personalizing blood pressure management in septic shock. Annals of intensive care, 5(1), 41.

INDIVIDUAL TITRATION

- Tailored titration of catecholamines to each patient. Avoid wide fluctuations in MAP
- Establish an individualized target MAP goal based on the patient scenario
- Change alarm limits on the monitor to reduce nuisance alarms and to encourage nursing titration
- WEAN. Less is More.

SUMMARY

- Target a MAP of 65–70 mmHg in a patient with septic shock who does not have chronic hypertension
  - It may be reasonable for the patient with chronic hypertension to target a MAP of 80–85 mmHg
- Vasopressors are associated with adverse events.
- Liver dysfunction, mesenteric ischemia, or AKI that can be associated with septic shock may not only result from the disease, but also from excessive use of vasopressors.
- MAP target as low as 60 mmHg may be reasonable to reduce vasopressor requirement.
- Studies have demonstrated poor compliance with MAP goals
- Establish an individualized target MAP goal based on the patient scenario

BE A WEAN-ER

Per the Surviving Sepsis Guidelines, which of the following represents the target MAP goal for patients with septic shock

A) MAP ≥ 65 mm Hg

B) MAP ≥ 80 mm Hg

C) Targeted therapy based on comorbid conditions

D) SBP ≥ 90 mm Hg

Answer A is the correct answer because all others do not result in significant differences in mortality and allow for auto regulation of organ systems.

All patients with septic shock and a history of hypertension should receive a higher MAP goal.

A) True

B) False

Answer B is the correct answer because there is no difference in mortality rates in patients receiving the standard lower MAP goal and the higher MAP goal. Care should be tailored and individualized depending on the patient scenario.

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QUESTIONS?