Study Synopsis

The Problem: A low blood pressure is one of the hallmarks of all forms of shock but does not define it. However, as hypotension worsens, it contributes to inadequate to tissue perfusion. While certain therapies for shock are cause-specific, correction of low blood pressure is uniform. Fluids to restore intravascular volume and **vasopressors** to increase blood pressure are used in an attempt to restore organ perfusion and function.[1] To date, no study has conclusively addressed the issue of vasopressor dosing. Accordingly, prescription of targets for vasopressor use are variable and arbitrary.[2 3] Suboptimal dosing of vasopressors may translate in increased mortality and morbidity, but the opportunity to get it right means saving lives and increased quality of life. A more liberal dosing strategy may lead to more physiological blood pressure levels and improved tissue perfusion while a more restrictive approach may minimize vasopressor-induced adverse effects. Because vasopressors are systematically given to a very vulnerable patient population, there exists little to no margin of error. The OVATION program of research is conducted under the auspices of the Canadian Critical Care Trials Group (CCCTG) and is endorsed by various organizations like the Institute for Safer Medication Practices (ISMP) and the Canadian Critical Care Society. It addresses targets for vasopressor therapy in shock. We propose a study, reflecting usual care, which will include patients who suffer from multiple categories of shock, excluding only patients with certain types of shock that clearly would not benefit from vasopressors (see planned inclusion and exclusion criteria).

Research Question: In critically ill patients in shock, does titrating vasopressors to higher (MAP 75 to 80 mmHg) vs. lower blood pressures (MAP 60 to 65 mmHg) result in reduced 90-day mortality?

Study Design: A multi-center, prospective, parallel group, randomized study of 4000 patients (see study flow diagram).

Setting: Approximately 30-40 ICUs in Canada, the United States, France, and other countries.

Study Population: Inclusion Criteria - We will randomize critically ill patients who are expected to require vasopressors for at least 6 hours despite fluid resuscitation. We will include patients who meet all of the following criteria: 1) receiving vasopressors for shock at the time of eligibility; 2) older than 16 years of age at the time of eligibility; 2) under the direct care of the ICU team regardless of location; 3) have received a minimum of 30 mL/kg of intravenous fluids (2100 mL for a 70 kg patient) before enrolment OR the most responsible physician has good reasons to believe that more fluid resuscitation is no longer required and could be harmful; and 4) the treating physician believes will need vasopressors for at least 6 hours once enrolled.

Exclusion Criteria - We will exclude patients who meet at least one of the following criteria: 1) have received vasopressors for more than 24 consecutive hours; 2) are judged by the treating physician to be in obvious cardiogenic shock after an acute myocardial infarction (based on new ST segment elevations on ECG or obvious echocardiographic findings); 3) have obvious haemorrhagic shock as a consequence of a clearly identified source of blood loss; 4) require vasopressors after cardiac surgery as a result of cardiopulmonary bypass-induced hypotension; 5) require catecholamine therapy for angioedema; 6) require catecholamine therapy for intracranial hypertension; 7) the attending team has agreed to withhold or withdraw life sustaining care or patients who are moribund (not expected to be in ICU for more than 48 hours due to imminent death); 8) concurrent enrollment in interventional trials when co-enrollment is not allowed (this will be addressed case by case); and 9) prior randomization in this study.

Study Interventions: Patients will be randomly allocated to receive vasopressors titrated to a MAP of 75 to 80 mmHg or 60 to 65mmHg. Vasopressor selection and titration algorithms are left at the discretion of the treating team.

Outcomes: The **primary outcome** will be **90-day mortality**. As **secondary outcomes**, we will measure functional autonomy, cognitive decline, cardiac arrhythmias, myocardial injury, digit necrosis, bowel ischemia, venous thromboembolic events, time-to-mobilization, feed intolerance. We will also document, as **tertiary mechanistic outcomes**, time-to-lactate clearance, and time-to-resolution of organ dysfunctions. Follow-up will end at 6 months.

Significance: Vasopressors are potent medications that are systematically administered to the most vulnerable patients. There is no margin of error with this patient population. The risk of suboptimal vasopressor use is increased mortality and morbidity while the opportunity to get it right is to save lives and reduce suffering. Because they have been a part of usual care for so long, we do not question our highly arbitrary and variable practices regarding dosing of vasopressors. This would be unacceptable for a new drug it is also unacceptable for vasopressors. A strength of this program is that its success is not contingent upon a specific result since we are comparing interventions that are constituents of standard care. There is no wrong answer. Moreover, because vasopressors are inexpensive and readily available in every country, the results will be applicable in high income and low income societies. Finally, vasopressors are used in many different settings. Although this OVATION study is targeting distributive shock (the dominant indication for vasopressors), the results will provide valuable information about expected risks and benefits in other settings such as intra-operative care, other forms of shock, neurocritical care etc. For all of these reasons, the OVATION Study will contribute to better, safer care of the critically patients.

Status: The pilot study is underway at several centers committed to the definitive study. We are more than 3/4 through recruitment for the pilot study and will complete this phase of OVATION 1 year ahead of schedule. So far, there have been no safety concerns and adherence with the protocol has been good. We are planning to submit to CIHR in March 2014 for funds to support the definitive study. The OVATION Executive Committee consists of Daren Heyland (Director of the Clinical Evaluation Research Unit at the Kingston General Hospital, methods center for the study), Maureen Meade, Paul Hébert and François Lamontagne. This trial is endorsed by and conducted under the auspices of the Canadian Critical Care Trials Group. For more information regarding study progress please visit our website (http://ovation.ccctg.ca/). We are actively recruiting additional centers to join this research program. Interested centers should contact the Principal Investigator.

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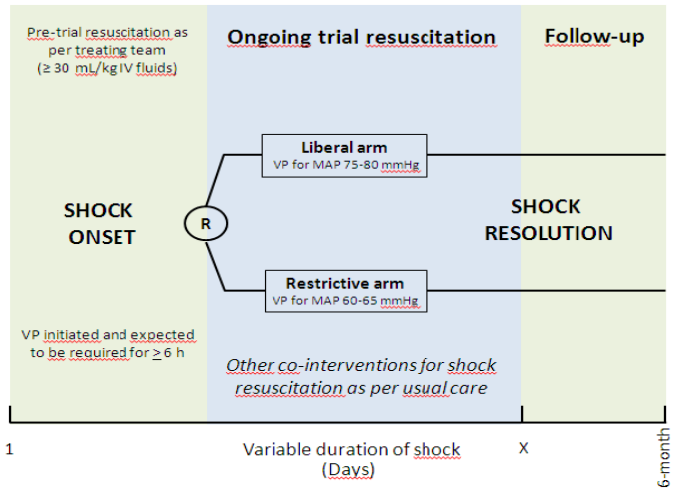
Study Flow Diagram



References

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2. Lamontagne F, Cook DJ, Adhikari NK, Briel M, Duffett M, Kho ME, et al. Vasopressor administration and sepsis: a survey of Canadian intensivists. J Crit Care 2011;26(5):532 e1-7.

3. St-Arnaud C, Éthier J-F, Hamielec C, Bersten A, Guyatt G, Meade M, et al. Prescribed targets for titration of vasopressors in septic shock: a retrospective cohort study. Canadian Medical Association Open Access Journal 2013;1(4):E127-E33F.

This study is registered at ClinicalTrials.gov
Identification #: NCT 01800887