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Do the current findings for hemodynamic optimization of the post-cardiac arrest patient take us out of our arterial pressure comfort zone?

Sarah M. Perman, MD, MSCE^{*,1} and David F. Gaieski, MD, FCCM²

¹Department of Emergency Medicine. University of Colorado, School of Medicine.

²Department of Emergency Medicine. Jefferson Medical College.

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In the current era of post-cardiac arrest management, clinicians and researchers continue to search for the next best therapeutic option that will right the course of the neurologically injured survivor of cardiac arrest to optimize outcomes. While novel therapies have been shown to impart neurologic protection and classic cardiovascular interventions have imparted better survival, the holy grail of post-arrest therapy has yet to be elucidated and bundling of post-cardiac arrest care continues to prevail as the standard clinical regimen.¹ To that end, those who care for patients after resuscitation from cardiac arrest continue to investigate how to improve care bundles implemented in the emergency department and intensive care units in order to optimize neurologic recovery and reduce further injury.²

Extensive research has addressed the role of dysregulated cerebrovascular autoregulation in brain injury and specifically in the global anoxic encephalopathy that is central to the pathophysiology of cardiac arrest.^{3,4} Researchers have determined that cerebral perfusion pressure is directly affected by this autoregulatory disruption and in combination with cerebral edema secondary to anoxic injury can result in overall impaired cerebral perfusion.³ This pathophysiology suggests an increase in overall mean arterial pressure (MAP) as a potential mechanism for driving increased cerebral perfusion pressures and thus cerebral perfusion,^{5,6} and that hypotension immediately after cardiac arrest will result in adverse outcomes.⁷ While this description of the physiology makes biological sense and retrospective observational data has been in support,⁸ prospective data to support increased MAP as a means of improving patient neurological outcomes are not in abundance. Early work by the study team did explore the association between MAP and neurologic recovery and found that mean MAP >70 mmHg was associated with a good neurologic recovery (Cerebral Performance Category of 1 or 2); however, they cite their small sample size and lack of uniform post-arrest care applied to this cohort (variable utilization of therapeutic hypothermia/targeted temperature management) as a weakness.⁹ This leads directly to the

*Corresponding author Sarah M. Perman, MD MSCE, Department of Emergency Medicine, University of Colorado, School of Medicine, 12401 E. 17th Avenue, Leprino Building, Aurora CO 80045, 720.4848.559, sarah.perman@ucdenver.edu.

natural next question: would this similar association be observed if all other facets of the standard post-arrest care bundle were held uniform.

In this issue of *Critical Care Medicine*, Dr. Brian Roberts and colleagues present compelling results from a multi-site prospective cohort study entitled “Association between elevated mean arterial blood pressure and neurological outcome after resuscitation from cardiac arrest: Results from a multicenter prospective cohort study”.¹⁰ Roberts et al. created a prospective Utstein style registry of both in and out of hospital cardiac arrest patients treated at 6 US sites. Among various classic exclusion criteria, patients in this analysis were also excluded if they had suffered a traumatic cardiac arrest or had presumed sepsis as the etiology of their arrest event. Additionally, the authors did not include patients with persistent hypotension (mean MAP < 70 mmHg) for the initial 6 hours after ROSC as this duration of hypotension in the immediate post-arrest period has already been shown to impart poor outcomes. The study team identified *a priori* a mean MAP of 70–90 mmHg versus a mean MAP of >90 mmHg as the predictor variables. The primary outcome identified in this study was a good neurological outcome at hospital discharge, defined as a modified Rankin Score (mRS) of ≤ 3.

Utilizing multivariable poisson statistical models, the authors determined that a mean MAP of >90 mmHg was an independent predictor of good neurological recovery at hospital discharge with a relative risk of 2.46 (95% CI 2.09–2.88). At baseline, the cohorts had a few notable differences. For example, the lower MAP group was older, had a longer duration of CPR and a higher incidence of withdrawal of life sustaining therapy (WLST), which might indicate a sicker cohort. The authors were able to account for patient and arrest factors in their analysis; however, the increased incidence of WLST in the lower MAP cohort was not taken into account. Interestingly, the authors do describe a dose response increase in the probability of good neurologic outcome by mean MAP over 10 mmHg intervals, with the best neurologic recovery determined when the mean MAP was greater than 100 mmHg, further supporting the investigators’ central theory that higher mean MAP is correlated with better recovery. Of important note, the authors found no difference in the association between mean MAP and neurologic outcome when accounting for vasopressor use or for escalating vasopressor dose. Finally, and perhaps most intriguing, the authors demonstrated that higher mean MAP values were most significantly associated with improved neurologic outcomes in patients with baseline hypertension, which may produce chronic alterations in cerebral autoregulation.

The work described in this manuscript is consistent with multiple prior studies utilizing retrospective data and from smaller cohorts. In Beylin *et al.*, investigators demonstrated that in a retrospective cohort of post-cardiac arrest syndrome patients, higher mean MAP at measured time points after ROSC was associated with better neurologic recovery at hospital discharge.⁶ However, they note that the utilization of vasopressors was negatively correlated with survival, a difference in comparison to the data presented by Roberts *et al.* Additionally, Ameloot and colleagues also reported in small prospective cohort that the best MAP range for optimal cerebral oxygenation is between 87–101 mmHg, again comparable with the results put forth by Roberts *et al.*⁵ There appears to be consensus that higher MAP in the

immediate post-ROSC time frame is associated with improved neurologic recovery after cardiac arrest, but the question that remains is *how to get there*.

In prior study, the utilization of vasopressor drugs for blood pressure management has been associated with worse outcome.^{6,9} But this current work shows that elevated mean MAP to >90 mmHg was protective irrespective of whether a vasopressor was administered or not. This begs the next question, if data prove that higher mean MAP is associated with better outcome, and vasopressors are not associated with poor neurologic recovery, then should target MAP be elevated for post-cardiac arrest patients, including administration of vasopressors for pharmacologic elevation to a goal of MAP >90 mmHG? The authors suggest that these should be the next questions posed: “Should we randomize patients to goal MAPs that are higher than standard critical care norms?” and “Should we administer vasoactive agents to achieve these targets?” While these are very valid questions, certainly, more data are required to systematically test these assumptions. We propose that a pragmatic trial, incorporating the patients’ pre-arrest baseline blood pressure measurements with the pre-determined post-arrest MAP target, should be conducted. Investigators will need to delineate the pharmacologic agents by which patients should arrive at those target MAP goals, and potentially, incorporate a control arm requiring pharmacologic management to maintain a MAP > 70 mmHG. Of note, in such a trial special attention must be applied to neuroprognostication, timing of decision-making, and most notably the utilization of WLST as these must remain uniform in order to accurately measure outcome of any interventions exploring neurologic recovery in post-cardiac arrest patients. While we suggest that this study is potentially the next step in formally answering the question pertaining to target MAP and how to achieve this, we recognize that this may come with some trepidation.

Vasopressors are not without risk and applying pharmacologic dosing of such drugs to optimize blood pressure to a novel target (i.e. higher than standard MAP requirements in critical care) may cause alarm. However, the prior literature, reaffirmed by this work by Roberts et al.,¹⁰ indicate that optimizing one of the core hemodynamic measures for maintaining adequate cerebral perfusion in the injured, recently reperfused brain may confer improvements in neurologic recovery. While this might not be the “holy grail” of neurologic recovery, it is certainly attainable and could be a therapy employed uniformly across critical care environments without new equipment or significant training. To that end, further study is necessary to solidify a protocol for how to achieve higher MAP targets, personalized to each patient’s pre-arrest baseline blood pressure, in order to improve upon the current evidence-based interventions that comprise the post-cardiac arrest bundle of care with the overall goal of improving neurologic recovery for comatose survivors of cardiac arrest.

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