INDIAN SOCIETY OF HYPERTENSION

Hypertension Journal

Commentary

Blood-Pressure Management in Post-Cardiac Arrest Care: A Review of the BOX Trial

Kartika Gautam

Clinical Associate, Yashwant Singh Parmar Government Medical College, Nahan, Himachal Pradesh, India

Abstract

This trial examined the optimal mean arterial blood pressure (MAP) target for comatose survivors of out-of-hospital cardiac arrest. In a double-blind, parallel-group design, the study enrolled Danish ICU patients who had a sustained return of spontaneous circulation (ROSC) after cardiac arrest. Participants were randomized to a higher MAP target (> 77 mmHg) or a standard MAP target (> 63 mmHg). Temperature control was maintained at 36°C for 24 hours, with mechanical ventilation and sedation. Neurological outcomes were assessed by attending physicians. The intervention protocol adopted a three-stage approach for MAP achievement, utilizing volume resuscitation, norepinephrine, and dopamine infusion as needed. The pharmacologic circulatory support was quantified using the vasopressor–inotropic score. The study concluded that there was no significant difference in the rates of death or severe disability between the two MAP target groups, suggesting that a higher MAP target does not improve the neurological outcome. The strengths of the trial include its methodological rigor and low attrition rate, with limitations related to its generalizability due to the single-country, two-centers setup.

Keywords: Arterial blood pressure, Cardiac Arrest, Post-Resuscitation Care

DOI: 10.61081/htnj/23v9i206

INTRODUCTION

Cardiac arrest is a leading cause of mortality and morbidity globally. The post-resuscitation period is critical, with blood-pressure management being a cornerstone of care for comatose survivors. The Blood-Pressure and Oxygenation Targets in Post-Resuscitation Care (BOX) Trial[1] addresses an essential clinical question: does a higher mean arterial pressure (MAP) target improve outcomes in this patient population?

Following a cardiac arrest, the restoration of spontaneous circulation brings forth a new set of challenges. Among these, maintaining adequate cerebral perfusion is paramount. Current guidelines suggest keeping MAP above 65 mmHg, but evidence for specific targets is limited, and higher targets may be necessary to ensure organ perfusion when autoregulation is impaired. For all purposes sustained ROSC was taken when chest compressions have been not required for 20 consecutive minutes and signs of circulation persist.

Corresponding author
Kartika Gautam, Clinical Associate, Yashwant Singh Parmar Government Medical College, Nahan, Himachal Pradesh, India,
Email: kartikagautam622@gmail.com

The BOX Trial's clinical question is significant because it may validate or contest existing practices, providing evidence for the optimal MAP target. The decision on MAP targets has profound implications for survival rates and neurological outcomes.

TRIAL DESIGN AND METHODOLOGY

The BOX Trial, conducted across two tertiary Danish ICUs from March 2017 to December 2021, is a double-blind, parallel-group randomized clinical trial with a 2-by-2 factorial design, also incorporating oxygenation targets reported separately.

Inclusion criteria were out-of-hospital cardiac arrest survivors with a presumed cardiac cause, sustained return of spontaneous circulation, and unconsciousness upon hospital admission. Exclusion criteria were comprehensive, including potential pregnancy, uncontrolled bleeding, and known diseases reducing survival likelihood. The trial randomized 800 patients, achieving adequate power to detect a 10% absolute reduction in the primary outcome.

The intervention group had a MAP target of 77 mmHg, while the control group had a target of 63 mmHg. Blinding was implemented by calibrating the blood pressure monitors to read 10% higher or lower than the actual blood pressure. Both groups followed protocolized recommendations to achieve the MAP targets with

fluids, noradrenaline, and dopamine, alongside standardized neurological assessment and temperature management. The total amount of pharmacologic circulatory support was quantified by the Vasopressor-Inotropic Score.[2,3] Dosages of vasoactive drugs were obtained from electronic intensive care unit databases and maximal dose for a given time period was captured. A stepwise trial methodology is shown in figure 1.

Figure 1: Trial methodology for all patients.

Trial methodology

- For the duration of the trial, all patients received temperature control to maintain a temperature of 36ºC for 24 hours in accordance with guidelines for comatose patients who had had an out-of- hospital cardiac arrest.
- Patients were receiving mechanical ventilation and were sedated, primarily with the use of propofol and fentanyl.
- Temperature control was achieved with surface cooling (CritiCool and Allon, Belmont Technologies) or with intravenous devices (Thermogard XP and Cool Line Catheter, Zoll).
- After completion of the 24-hour period of temperature control, the core temperature was gradually increased to normothermia with a rewarming rate of less than 0.5ºC per hour, and sedation was tapered.
- Assessment of neurologic outcomes was performed by the attending physician in accordance with guidelines.
- Trial Intervention - The protocol provided a recommendation for achieving the mean arterial blood pressure of 70 mm Hg in a three-stage approach:

1.volume resuscitation to a central venous pressure of 10 mm Hg,
2.norepinephrine infusion,
3.addition of a dopamine infusion for a maximal dose of 10 gg per kilogram of body weight per minute, if needed.

- The total amount of pharmacologic circulatory support was quantified as the vasopressor—inotropic score (higher scores indicate a higher degree of support)

RESULTS AND INTERPRETATION

The BOX Trial found no significant difference across any outcomes, including the primary composite of death or discharge with severe disability. Subgroup analysis revealed no differences in 90-days all-cause mortality across categories such as age, hypertension, or renal impairment.

These findings are consistent with the hypothesis that a MAP range higher than current standard practice does not confer additional benefit in terms of mortality and neurological function. The study's strengths include its innovative design, good treatment separation, and minimal loss to follow-up.

Primary Outcome

The primary outcome was death from any cause or a hospital discharge with a Cerebral Performance Category (CPC) of 3 or 4 within 3 months, showed no significant difference between the high-target (77 mmHg) and low-target (63 mmHg) groups. Specifically, 34% in the high-target group and 32% in the low-target group experienced these outcomes.

This lack of significant difference indicates that a higher MAP target did not reduce the risk of death or severe disability. It challenges the assumption that higher blood pressure targets might be beneficial in ensuring better cerebral perfusion post-cardiac arrest.

Table 1: Cerebral Performance Category[4]

Category	Level of Cerebral Performance	Description
1	Good cerebral performance	Conscious, alert, able to work, might have mild neurologic or psychologic deficits.
2	Moderate cerebral disability	Disabled but independent, able to perform daily life activities with some support.
3	Severe cerebral disability	Conscious, dependent on others for daily support because of impaired brain function.
4	Coma or vegetative state	Any degree of coma without the presence of all brain death criteria, unresponsive, no interaction with the environment.
5	Brain death	Criteria of brain death present, unresponsive and unarousable.

Secondary Outcomes

The study also evaluated several secondary outcomes such as death from any cause, scores on CPC, modified Rankin scale and Montreal Cognitive Assessment at 3 months and neuron-specific enolase levels at 48 hours.

At 90 days, the mortality rates were similar in both groups: 31% in the high-target group and 29% in the low-target group.

The median CPC, modified Rankin scale scores, and Montreal Cognitive Assessment scores were comparable between the two groups. These tools, which assess neurological function and disability, showed no significant benefit of higher MAP targets.

The median neuron-specific enolase levels, a marker of neuronal damage, were also similar, further corroborating the primary outcome results.

Table 2: Montreal Cognitive Assessment Scores[5]

Score Range	Cognitive Function	Description
26-30	Normal	No evidence of cognitive impairment.
18-25	Mild Cognitive Impairment	May indicate mild cognitive impairment.
10-17	Moderate Cognitive Impairment	May indicate moderate cognitive impairment.
0-9	Severe Cognitive Impairment	May indicate severe cognitive impairment.

Table 3: Modified Rankin Scale (mRS)[6]

Score	Level of Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Adverse Events

Importantly, the study found no significant difference in adverse events, including infections, arrhythmias, bleeding, electrolyte disorders, metabolic disorders, and seizures between the two groups. This finding is crucial as it suggests that a higher MAP target does not increase the risk of such events, which are of concern in patients receiving intensive care.

Interpretation of Results

These results suggest that for comatose survivors of out-of-hospital cardiac arrest, aiming for a MAP target of 77 mmHg does not offer a survival or neurological benefit over a MAP target of 63 mmHg.

This finding is significant in guiding clinicians on blood pressure management in a sensitive and critical patient population. It reinforces that maintaining a MAP above 65 mmHg, as currently practiced, is adequate.

The lack of difference in outcomes also implies that the body's tolerance to a range of MAP levels post-cardiac arrest might be wider than previously assumed, provided it is within a clinically acceptable range.

This trial's results contribute valuable evidence to a previously under-researched area in post-cardiac arrest care, filling a gap in clinical knowledge with robust, randomized trial data.

Discussion and Critical Analysis

The trial's methodology is robust, with a well-designed, multi-center approach and strong randomization protocol. However, the study's generalizability may be limited, as it was conducted exclusively in Denmark. The use of dopamine as an inotrope and a 10 mm Hg difference in MAP might not be sufficient to discern a difference in outcomes, and the MOCA scores were only available for a subset of patients, which could affect the interpretation of neurological outcomes.

Despite these limitations, the BOX Trial is an invaluable addition to the evidence base, suggesting that maintaining a MAP of 65 mmHg may be adequate for survivors of out-of-hospital cardiac arrest, aligning with current practices. It also challenges the notion that higher MAP targets are universally beneficial, reinforcing the need for individualized patient care.

Implications for Clinical Practice

The findings suggest that clinicians should continue to aim for a MAP of greater than 65 mmHg, as higher targets do not significantly reduce death or poor neurological status. The BOX Trial supports the notion that the current MAP targets are safe and appropriate for most patients.

However, the study also opens avenues for further research, particularly in different patient subsets or with other MAP ranges. Additionally, it calls for an evaluation of other interventions that may improve outcomes in this patient population.

CONCLUSION

The BOX Trial provides compelling evidence that a MAP target of 77 mmHg does not yield better outcomes than a target of 63 mmHg for comatose survivors of out-of-hospital cardiac arrest. Higher MAP targets do not translate to better outcomes in comatose survivors of cardiac arrest. Its findings affirm the adequacy of current MAP targets and underscore the importance

of individualized care. As such, the trial's results should reassure clinicians about the safety of existing protocols and guide future research to refine post-cardiac arrest care further.

References

1. Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. New England Journal of Medicine. 2022 Oct 20;387(16):1456–66.
2. Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-Inotropic Score: Evolution, Clinical Utility, and Pitfalls. J Cardiothorac Vasc Anesth. 2021 Oct;35(10):3067–77.
3. Wernovsky G, Wypij D, Jonas RA, Mayer JE, Hanley FL, Hickey PR, et al. Postoperative Course and Hemodynamic Profile After the Arterial Switch Operation in Neonates and Infants. Circulation. 1995 Oct 15;92(8):2226–35.
4. Jennett B. Assessment Of Outcome After Severe Brain Damage A Practical Scale. The Lancet. 1975 Mar;305(7905):480–4.
5. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005 Apr 30;53(4):695–9.
6. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604–7.

How to cite this article: Gautam K, Blood-Pressure Management in Post-Cardiac Arrest Care: A Review of the BOX Trial. Hypertens J. 2023; 9(2): 52-55.
Source of support: Nil, **Conflicts of interest:** None