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IN PERSPECTIVE
Acute Coronary Syndromes

Blood pressure and oxygenation targets after out-of-hospital cardiac arrest-trial (BOX)

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Evidence before this study

Hypotension after a resuscitated out-of-hospital cardiac arrest (OHCA) is common, and may be due to post-arrest myocardial dysfunction and/or vasoplegia.[1] In patients with post-OHCA hypoxic ischaemic brain injury, cerebral blood flow autoregulation may be impaired resulting in a risk of cerebral hypoperfusion with a low normal mean arterial pressure (MAP).[2] Moreover, in observational studies, post-OHCA hypotension has been associated with a higher risk of mortality.[3,4] However, the potential benefits of routine higher MAP targets must be counterbalanced against the potential risks of higher doses of vasoactive medications including arrhythmogenesis, and higher systemic vascular resistance (SVR) inducing impaired cardiac output (CO) and coronary perfusion.

A recent pooled analysis of the NEUROPROTECT and COMACARE trials included 235 post-OHCA patients who were randomized to MAP targets of 65 mmHg or 80/85–100 mmHg for the first 72 h after admission reported a lower 72-h troponin area under the curve with no difference in arrhythmias despite higher vasoactive use in the high MAP target arm. The study was not powered for clinical outcomes.[5]

Contribution to clinical practice

The optimal MAP target in patients with a resuscitation OHCA remains unknown. The European Resuscitation Council post-cardiac arrest Care Guideline recommends to avoid MAP <65 mmHg; however, this target is a weak recommendation based on low quality evidence.[6]

Aim of the study

The aim of the trial was to evaluate the difference in a target MAP of 63 vs. 77 mmHg on CO, SVR, and pulmonary capillary wedge pressure.[7]

Study design

The BOX trial was a double-blind, multicentre factorial trial that randomized comatose post-OHCA patients to a target MAP to 63 or 77 mmHg, and to a liberal vs. restrictive oxygenation target.[8] It enrolled 8000 patients from two centres in Denmark. Blinding was achieved through a programmed calibration factor in the haemodynamic monitoring modules that was adjusted in a 1:1 randomization to show a BP value either lower or higher than the patients' actual BP, such that targeting 70 mmHg during treatment in both groups will result in an intended blinded comparison of 63 and 77 mmHg.

Study patients

Selected inclusion criteria included: age ≥18 years, OHCA of presumed cardiac cause, sustained return of spontaneous circulation for >20 min, Glasgow Coma Scale <8, >4 h from return of spontaneous circulation to randomization.

Selected exclusion criteria: In hospital cardiac arrest, unwitnessed systole, >4 h from return of spontaneous circulation to randomization to randomization; systolic blood pressure <80 mmHg despite fluids, vasopressor, and/or ionotropic support.

Other salient features/ characteristics

All patients underwent targeted temperature management at 36°C. Pulmonary arterial catheter measurements were protocolized for first 48 h.

Principal finding

A total of 789 patients were randomized, among whom, 85% presented with a shockable rhythm, 86% had bystander cardiopulmonary resuscitation (CPR), the mean time to return of spontaneous circulation was 18 min, and 45% presented with ST-segment elevation.[8]

The mean difference in MAP was 10.5 mmHg, which was primarily achieved with higher dosages of vasoactive agents.

- There was no difference in the primary outcome of death within 90 days or hospital discharge with a poor neuro cerebral performance score (CPC 3 or 4) between the high (34%) vs. low MAP (32%) arms.
- There were no differences in secondary outcomes including all-cause death, acute kidney injury requiring renal replacement therapy (10% in both arms), median neuron-specific enolase at 48 h, or in Montreal Cognitive Assessment scores at 90 days measured among survivors. Adverse events including the incidence of arrhythmias were similar between treatment arms.

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In perspective

In the largest randomized trial focused on target blood pressure during management of post-cardiac arrest syndrome, the findings indicate that routine treatment to a higher MAP target does not improve clinical outcomes. The trial population was representative of care in Denmark with a very high proportion of initial shockable rhythm with bystander CPR resulting in a short time to return to spontaneous circulation (21 min) and a remarkably good median CPC at follow-up (one in both groups). An algorithm for blinded targeting of different BP targets in the two groups is a particular strength of this randomized trial. The achievement of a 10.5 mmHg differential BP between the two treatment arms supports adherence to implementation of the protocol with a meaningful test of the main hypothesis. Treatment with a lower MAP target appeared safe and reduced the overall dosing of vasopressors.

As such, the BOX randomized trial provides high quality evidence that a MAP of 63–65 mmHg is a reasonable initial target in the management of this high-risk population; though the target may need to individualized in some patients with persistent end-organ hypoperfusion or in those who develop cerebral oedema. These trial results may be easily integrated into clinical practice. Future studies may be warranted to evaluate higher MAP targets in a study population with a higher baseline potential for severe anoxic brain injury. Although given the directionality of the observed result, the likelihood of a benefit of higher MAP target appears unlikely, the trial was designed with adequate power for a ∼26% relative risk reduction and thus it is possible that a smaller, but clinically relevant, effect size could have been missed.

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