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WHAT'S NEW IN INTENSIVE CARE

Optimal oxygen and mean arterial blood pressure targets after cardiac arrest

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Most resuscitated cardiac arrest patients die in the intensive care unit due to hypoxic brain injury [1]. The pathophysiological process includes disturbed cerebral autoregulation resulting in inadequate blood flow and ischemia, and means to alleviate this could include giving more oxygen or increasing the mean arterial pressure (MAP) with vasopressors [2]. Supplemental oxygen may result in hyperoxia, which has been associated with harmful reactive oxygen species [3]. Whether limiting oxygen use could decrease brain injury after cardiac arrest has received much attention. Pilot studies have shown through biomarker levels that targeting a higher MAP than the recommended 65 mmHg may alleviate brain and cardiac injury [4]. The lack of large randomized controlled trials on MAP and oxygen has been a major shortcoming [5]. In 2022, the BOX and EXACT trials (Table 1) were published, with major ramifications for post-cardiac arrest management [6–9].

The BOX trial

The BOX (Blood pressure and OXygenation targets after out-of-hospital cardiac arrest) randomized clinical trial with a 2-by-2 factorial design was performed at two Danish tertiary hospitals from 2017 to 2022 [7–9]. Two blood pressure targets, two oxygenation targets, and the duration of fever management with a device were compared in 789 comatose out-of-hospital cardiac arrest patients. In the sample, the bystander cardiopulmonary resuscitation (CPR) rates and proportion of patients with ventricular fibrillation were close to 90%. Using a novel method, the blood pressure intervention was double-blinded: the blood pressure monitoring devices were randomly offset to display either − 10% or + 10% of the target (70 mmHg), resulting in targeting a MAP of 63 or 77 mmHg. The oxygenation intervention was an open-label randomization to either a restrictive oxygen target of a PaO_2 of 9–10 kPa (68–75 mmHg) or a liberal oxygen target of a PaO_2 of 13–14 kPa (98–105 mmHg). All patients were also randomized 1:1 to active fever control with an automated feedback temperature control device for 36 or 72 h following the return of spontaneous circulation (ROSC). The primary outcome of all interventions was a composite of death from any cause or hospital discharge with a cerebral performance category of 3 or 4 within 90 days. The blood pressure, oxygen, and fever management interventions resulted in similar primary and all secondary outcomes (primary endpoint for blood pressure targets: HR [95% CI] 1.08 [0.84–1.37], $p=0.56$); primary endpoint for oxygen targets HR [95% CI] 0.95 [0.75–1.21], $p=0.69$). In conclusion, the current evidence suggests that a MAP target of 63 mmHg during intensive care unit (ICU) care in patients admitted comatose after being resuscitated from an out-of-hospital cardiac arrest (OHCA) seems safe. Restrictive or liberal oxygen targets within the recommended range appear equally safe [5].

The EXACT trial

The EXACT (rEduction of oXygen After Cardiac arrest Trial), a parallel-group randomized clinical trial that was performed in 2 emergency medical services and 15 hospitals in Australia [6]. It compared two oxygenation targets in the prehospital and emergency department (ED) phases of CPR post-resuscitation care of 425 comatose presumed cardiac OHCA patients with bystander rates of 80% and of whom 60% had a shockable initial rhythm. Patients were randomized to receive oxygen titration to achieve an oxygen saturation (SpO_2) of either 90–94% ($n=216$) or 98–100% ($n=212$) until ICU arrival. The

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Table 1 Characteristics of three recent trials on oxygen and MAP targets after cardiac arrest

Study	Patients	Intervention timing and duration of	Intervention arm target	Control arm target	Result	Comment	Impact on clinical management
BOX MAP trial	789 cardiac cause OHCA patients	Started at 2.5 h from OHCA and continued for the ICU stay	77 mmHg	63 mmHg	No difference in outcome	Major strength is blinded design	No reason to deviate from the current recommendation of targeting a MAP higher than 65 mmHg
BOX oxygen trial	789 cardiac cause OHCA patients	Started at 2.5 h from OHCA and continued for the ICU stay	9–10 kPa	13–14 kPa	No difference in outcome	Small difference in oxygen levels	No reason to deviate from the current oxygen target of 10–13 kPa
EXACT trial	425 cardiac cause OHCA patients	Started 30 min from ROSC and continued for 6 h	90–94 SpO_2	98–100 SpO_2	10% higher mortality in the lower oxygen arm	Premature stopping of trial may increase risk of chance findings	Targeting peripheral oxygen saturations less than 95% is best avoided in the prehospital setting and the emergency department

ICU intensive care unit, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, SaO_2 oxygen saturation

study was not blinded. Importantly both the interventional targets were outside what the current recommendations are (i.e., SpO_2 of 94–98%) [5]. For most patients in the 98–100% group, oxygen titration did not occur until the ED due to the use of air-mix ventilators in the prehospital setting. Randomization in both groups occurred at a median of 36 min post-ROSC, and oxygen levels on arrival at hospital and at the ICU suggest that titration occurred in both groups with reasonable separation in SpO_2 and PaO_2.

The trial was stopped early due to the coronavirus disease 2019 (COVID-19) pandemic, the primary outcome showed lower survival to discharge in the group randomized to the lower oxygen target (38.3% vs 47.9%; difference − 9.6% [95% CI − 18.9 to − 0.2%]; unadjusted OR 0.68 [95% CI 0.46–1.00]; $p = 0.047$). The lower oxygen target group was twice as likely to experience a hypoxic episode during the intervention phase (31.3% vs 16.1%, $p < 0.001$). The study also showed a not statistically significant difference in mortality of those patients with a re-arrest without ROSC (10.8% vs 6.4%, $p = 0.25$). This trial indicates that early oxygen titration to an SpO_2 of less than 95% is unsafe in the early post-resuscitation phase of OHCA in comatose patients, particularly in the complex prehospital setting, where healthcare providers are restricted in equipment for administration and monitoring.

Take-home message

The current evidence does not suggest any clear benefit from deviating from current guidelines (i.e., targeting a paO_2 of 10–13 kPa and a MAP of higher than 65–70 mmHg) [10]. A meta-analysis comparing studies investigating a standard (60–70 mmHg) and higher MAP target (80–100 mmHg) after cardiac arrest is in progress, Preliminary analysis suggests that the current evidence from conducted trials can rule out a relative beneficial effect of more than 25% with a higher compared to a lower MAP target (Skrifvars, personal communication). Given outcome rate from ICU care of OHCA patients is generally in line in the range of 50–60%, this would translate into an absolute difference of 12–18% (equalling a number needed to treat of between 5 and 9). This may be an unrealistic effect size compared to other post-cardiac arrest interventions, such as targeted temperature management [11]. Observational data do suggest that the optimal MAP target in a patient with impaired cerebral autoregulation could be as high as 85–90 mmHg [12]. Larger trials on this topic are needed, also including patients with a non-cardiac cause of the arrest. With regard to oxygen, the challenge may be the non-linear U-shaped association between oxygen and outcome [13]. Although there may be no beneficial effect of targeting

oxygen levels beyond normoxia, the EXACT trial clearly shows that more liberal oxygen use may be the best approach if reliable oxygen monitoring is difficult, such as during transport or care in the ED [14].

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Declarations

Conflicts of interest
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