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RECENT ADVANCES IN ICU

Out-of-hospital cardiac arrest

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Cardiac arrest science continues to evolve and in the last two years many cardiac arrest clinical trials have been published in high-impact journals. In this manuscript we have selected 6 trials that have the potential to influence guidelines and clinical practice (Table 1).

The COCA trial (Calcium for Out-of-Hospital Cardiac Arrest, NCT04153435).

Although current guidelines do not recommend routine use of calcium in cardiac arrest [1], data from the United States of America indicate that it is used in about 25% of in-hospital cardiac arrests (IHCAs) [2]. In the COCA randomised clinical trial (RCT), 397 out-of-hospital cardiac arrest (OHCA) patients received up to two doses of 5 mmol calcium chloride or saline [3]. The trial was stopped early by a safety committee because of concerns of harm in the calcium group. The primary outcome, return of spontaneous circulation (ROSC), occurred in 19% of patients in the calcium group compared with 27% in the saline group (risk ratio (RR) 0.72, 95% CI 0.49–1.03; P = 0.09). A sub-analysis of patients with pulseless electrical activity (PEA), a group that is more commonly given calcium, also showed a signal for harm (ROSC 20% versus 39%; RR 0.51, 95% CI 0.26–1.0) [4]. These findings suggest that calcium should not be given to unselected patients in cardiac arrest. Guidelines continue to recommend calcium for cardiac arrest associated with hyperkalaemia [5], although there are no high-certainty data showing benefit even in this group.

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The DOSE VF trial (Double Sequential External Defibrillation for Refractory Ventricular Fibrillation, NCT04080986).

This cluster randomised trial compared double sequential (DSED) or vector change (VC) defibrillation with standard defibrillation (SD) for refractory ventricular fibrillation (VF) OHCA [6]. In DSED two defibrillators [pads in anterior-lateral and anterior–posterior (AP) positions] are used to deliver sequential shocks. In VC, single shocks were delivered with pad orientation in AP position. The rationale is that delivering current through a larger proportion of the myocardium will improve VF termination. The trial was stopped early because of logistical problems related to the coronavirus disease 2019 (COVID-19) pandemic. Of 405 patients randomized, 152 were also included in an earlier pilot study [7]. All received SD for the first 3 defibrillations, then received SD, VC or DSED. Survival to hospital discharge and termination of VF were improved with both DSED [adjusted relative risk (aRR) 2.21 (1.33–3.67)] and VC [aRR 1.71 (1.01–2.88)] compared with SD. ROSC and modified Rankin Scale (mRS) score were also improved with DSED, but results were not statistically significant for VC. Whether DSED is superior to VC is unclear. This trial suggests that DSED or VC may be more effective than SD for patients with refractory VF. More trials would be useful to validate these findings, and to compare DSED to VC. In the meantime, VC defibrillation is already suggested in current guidelines [1] and, unlike DSED, does not require additional resources.

The INCEPTION trial (Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest trial, NCT03101787).

If advanced life support (ALS) interventions fail to achieve ROSC, extracorporeal cardiopulmonary resuscitation (eCPR) can restore perfusion to vital organs while the cause of cardiac arrest is identified and treated. Two previous RCTs were terminated prematurely after

Table 1 Summary of important cardiac arrest studies

Trial-intervention	Key findings	Clinical implications
COCA-calcium or saline in OHCA	Decreased ROSC with calcium, although did not achieve statistical significance	Calcium should not be used routinely for cardiac arrest. It continues to be used for cardiac arrest associated with hyperkalaemia
DOSE VF/SD-VC or DSED for refractory VF in OHCA setting	Improved survival with DSED and VC compared with SD. Improved mRS with DSED compared with SD	Either DSED or VC may be useful when VF is refractory to at least 3 shocks
INCEPTION trial-eCPR versus conventional CPR in refractory OHCA	No difference in 30-day survival with favourable functional outcome	Consider eCPR in selected patients and selected centres when ROSC cannot be achieved with conventional CPR
EXACT-post-ROSC oxygen titration to oxygen saturation of 90–94% or 98–100%	Increased mortality and hypoxic events in the 90–94% group	Oxygen titration to a conservative target of 90–94% is harmful in the prehospital setting
TTM2-temperature control at 33 °C versus 37.5 °C	No difference in 6-month mortality	Change from a strategy of hypothermic control to one of normothermia/prevention of fever
BOX blood pressure-MAP 63 mmHg versus 77 mmHg	No difference in composite outcome of death or poor functional outcome	Continue with individualised MAP targets
BOX Oxygenation-PaO_2 9–10 kPa versus 13–14 kPa	No difference in composite outcome of death or poor functional outcome	Continue to target a PaO_2 10–13 kPa as suggested in ERC-ESICM guidelines

OHCA out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *VC* vector change defibrillation, *DSED* double sequential defibrillation, *VF* ventricular fibrillation, *mRS* modified Rankin scale score, *MAP* mean arterial pressure, *ERC-ESICM* European Resuscitation Council-European Society of Intensive Care Medicine

pre-determined interim analyses—one because of superiority of eCPR [8] and the other because of its futility [9]. In the more recent INCEPTION trial, 160 OHCA patients with an initial shockable rhythm and who failed to achieve ROSC after 15 min of ALS were randomised to receive eCPR (starting after arrival in the emergency department) or conventional CPR [10]. Patients with an expected interval of more than 60 min between cardiac arrest and initiation of the cannulation procedure were excluded. Of the 70 patients assigned to the eCPR group, cannulation and restoration of circulation was successful in 46 (66%). Fewer patients in the standard group survived to intensive care unit admission [36% versus 81%, odds ratio (OR) 0.1 (95% CI 0.1–0.3)] but there was no significant difference in 30-day survival with favourable functional outcome (the primary outcome—eCPR 20% versus 16%, OR 1.4, 95% CI 0.5–3.5, P = 0.52). The effectiveness of eCPR is likely highly dependent on patient selection and the experience of clinicians and centres delivering the intervention; as such, it is a challenging intervention to study in an RCT. The results of the INCEPTION study are unlikely to change the most recent treatment recommendation made by the International Liaison Committee on Resuscitation (ILCOR): 'We suggest eCPR may be considered as a rescue therapy for selected patients with OHCA when conventional CPR is failing to restore spontaneous circulation in settings where this can be implemented (weak recommendation, low certainty of evidence) (https://costr.ilcor.org/document/extracorporeal-cardiopulmonary-resuscitation-ecpr-for-cardiac-arrest-als-tfsr).

The EXACT trial (rEduction of oXygen After Cardiac arrest Trial, NCT03138005).

To prevent the harmful effects of hyperoxia, EXACT examined two strategies of oxygen titration in the early phase of post-resuscitation care in two prehospital and 15 emergency department (ED) settings [11]. Haemodynamically stable OHCA patients, with sustained ROSC and an oxygen saturation (SpO_2) of > 94%, were randomised to a target a SpO_2 of 90–94% or 98–100%. The trial was stopped early because of the CoVID-19 pandemic and reported on 425 of 428 randomised patients. The SpO_2 differed between groups. The primary outcome of survival to hospital discharge was lower in the group with a target SpO_2 of 90–94% (38.3% vs 47.9%; difference, −9.6% [95% CI −18.9 to −0.2%]; unadjusted odds ratio, 0.68 [95% CI 0.46–1.00]; P = 0.047). This treatment group also had more hypoxaemic episodes (31.3% vs 16.1%, P < 0.001), a finding that was also seen in the EXACT pilot study [12]. These findings suggest that early titration of oxygen to a SpO_2 target of 90–94% should be avoided, particularly in the prehospital setting where SpO_2 is the only available measurement and titration of oxygen is limited.

The TTM2 trial (Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest, NCT02908308).

The optimal target temperature for comatose post-cardiac arrest patients remains contentious. In the TTM2 trial, 1850 comatose patients with ROSC after all-rhythm OHCA were randomised to temperature control at 33 °C for 28 h versus ≤ 37.5 °C [13]. Cardiac arrests of likely

non-cardiac cause and unwitnessed cardiac arrest with an initial rhythm of asystole were excluded. Temperature was monitored continuously in all patients and 46% of the patients in the normothermia group received cooling with a device. Death at 6 months, the primary outcome, occurred in 50% of patients in the hypothermia group versus 48% in the normothermia group (RR 1.04; 95% CI 0.94–1.14; P = 0.37). The median time from cardiac arrest to a temperature of 34 °C in the hypothermia group was approximately 5 h. This is consistent with most clinical studies of temperature control after cardiac arrest and may be outside the much shorter therapeutic window that has been demonstrated in animals [14]. ILCOR now suggests preventing fever by targeting a temperature $\leq$ 37.5 °C for patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low-certainty evidence) [15]. The same recommendation has been made by the European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) [16].

The BOX Trial (Blood Pressure and Oxygenation Targets in Post-resuscitation Care, NCT03141099).

The optimal blood pressure and oxygen targets after ROSC remain uncertain. Using a 2×2 factorial design, the BOX RCT compared two mean arterial pressure (MAP) targets (63 mmHg and 77 mmHg) [17] and two oxygenation targets (9–10 kPa and 13–14 kPa) [18] in 789 comatose post-cardiac arrest patients. By adjusting the internal calibration of the invasive blood pressure monitors, the displayed MAP was either 10% higher or 10% lower than the actual MAP. Clinicians targeted a MAP of 70 mmHg but were blinded to the actual MAP. A primary outcome event (composite of death or poor functional outcome at 90 days) occurred in 34% of patients in the high-target group and in 32% in the low-target group [hazard ratio (HR) 1.08; 95% CI 0.84–1.37; P = 0.56]. The mean difference of 10.7 mmHg was smaller than the targeted 14 mmHg difference and may have been too small to affect clinical outcomes. Pending further data, it would seem reasonable to individualise MAP targets. In the oxygenation domain, a primary-outcome event occurred in 32% of patients in the restrictive-target group and in 33.9% in the liberal-target group (HR 0.95; 95% CI 0.75–1.21; P = 0.69). In oxygenation trials it can be difficult to maintain the target in the restrictive group and although separation between groups was successfully achieved, the PaO_2 in the restrictive group was at the upper end of the range. Ongoing large RCTs of oxygen targets in critically ill patients [e.g. Mega-ROX (ANZCTRN 12620000391976), UK ROX (ISRCTN13384956)] will include very large subsets of post-cardiac arrest patients and may help to inform the optimal oxygen targets in these patients. Pending further data, it may be reasonable to target an oxygenation target of 10–13 kPa as suggested in ERC-ESICM guidelines [16].

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