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EDITORIAL

Focus on post-resuscitation care

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In patients who are admitted to an intensive care unit after resuscitation from cardiac arrest (CA) mortality attains 60–70% [1]. Two-thirds of these deaths are due to hypoxic-ischaemic brain injury (HIBI) and occur mainly after 72 h, as a result of withdrawal of life-sustaining treatment (WLST) based on the prediction of a poor neurological outcome [2]. The second most common cause of post-resuscitation death, especially in the very early phase after return of spontaneous circulation (ROSC), is circulatory failure. Current research on post-resuscitation care focuses on interventions aimed at reducing these two important causes of morbidity and mortality after CA.

Temperature management and coronary angiography

Targeted temperature management (TTM) for 24 h after ROSC is recommended to reduce HIBI, but the optimal temperature is unclear [2, 3]. A recent multicentre pilot randomised clinical trial (RCT) assigned comatose survivors of witnessed out-of-hospital CA (OHCA) from ventricular fibrillation/ventricular tachycardia (VF/VT) to TTM at 32 °C ($n=52$), 33 °C ($n=49$) or 34 °C ($n=49$), see Table 1. Cooling was tolerated well, but 90-day neurological outcome did not differ among groups [4]. Patients cooled to 32 °C had lower rates of WLST due to severe HIBI. Cooling to this temperature may be the focus of further research.

Immediate coronary angiography is recommended in survivors of OHCA with ST-segment elevation (STE) on their electrocardiogram [1], but the benefit of this intervention after non-STE OHCA is uncertain. The multicentre COACT trial, which included 552 non-STE patients resuscitated from VF/VT OHCA, showed that an immediate vs. a delayed angiography strategy (median [IQR] 2.3 [1.8–3.0] vs. 121.9 [52.0–197.3] h from arrest) was not associated with higher 90-day survival (64.5 vs. 67.2%; $p=0.51$) [5]. Acute unstable coronary lesions were found in less than 20% of the patients in this trial. Future studies may focus on non-STE patients more likely to benefit from immediate percutaneous coronary interventions (PCI). A recent retrospective study on 1,410 resuscitated OHCAs also suggested that only patients with low risk of in-hospital death according to the Cardiac Arrest Hospital Prognosis score benefited from early PCI [6].

Oxygenation and ventilation, and cerebral perfusion

Observational evidence suggests that hyperoxia may be associated with worse neurological outcome after CA, while mild hypercapnia and higher mean arterial blood pressure (MAP) may be associated with better neurological outcome [2]. The COMACARE pilot multicentre RCT evaluated the feasibility of targeting low-normal (4.5–4.7 kPa) vs. high-normal (5.8–6.0 kPa) $PaCO_2$, normoxia (PaO_2 10–15 kPa) vs. moderate hyperoxia (PaO_2 20–25 kPa) and low-normal (65–75 mmHg) vs. high-normal (80–100 mmHg) MAP [7, 8] during the first 36 h after ROSC in 123 comatose patients resuscitated from

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Table 1 Design, findings and limitations of recent studies on post-resuscitation care

Study	Aims and design	Findings	Limitations
Lopez-de-Sa et al. [4]	To evaluate three levels of TTM (32, 33 and 34 °C) via endovascular cooling devices Comatose survivors of witnessed OHCA and initial shockable rhythm Multicentre 1:1:1 randomised trial Primary endpoint: survival with good neurological outcome, defined as a modified Rankin Score (mRS) ≤ 3, blindly assessed at 90 days	Patients included: 32 °C ($n=52$), 33 °C ($n=49$) and 34 °C ($n=49$) Patients with mRS ≤ 3 at 90 Days: 65, 66 and 66%, non-significant All levels of cooling were well tolerated Patients cooled to 32 °C had lower rates of WLST due to severe HIBI. Male gender and bystander defibrillation were associated with significantly higher hazard ratios of good neurological outcome	Small sample size, limited power Less patients randomised to 32 °C received bystander AED Unblinded application of TTM
Lemkes et al. [5]	To evaluate a strategy of immediate vs. delayed coronary angiography and PCI if needed Non-STE patients resuscitated from VF/VT OHCA Multicentre randomised trial Primary endpoint: survival at 90 days	Median [IQR] time to angiography: 2.3 [1.8–3.0] vs. 121.9 [52.0–197.3] h from arrest Shorter mean time to target temperature in the delayed group: 4.7 vs. 5.4 h (ratio of geometric means, 1.19; 95% CI, 1.04 to 1.36) No difference in primary endpoint: 176/273 (64.5%) in the immediate vs. 178/265 (67.2%) in the delayed angiography group, $p=0.51$	Acute unstable coronary lesions found in less than 20% of the patients Target temperature reached later in the immediate angiography group Patients in the delayed angiography group more likely to receive salicylates or a P2Y12 inhibitor (or both) Patients with shock or severe renal dysfunction excluded
Bougouin et al. [6]	To assess the value of the CAHP (Cardiac Arrest Hospital Prognosis) score (low 150, medium 150-200 and high risk > 200 points) in the decision for early coronary angiography Patients with OHCA of presumed cardiac cause Population-based registry Endpoint: survival at hospital discharge	Total 1410 patients included: 667 low, 469 medium, and 274 high risk Low-risk patients more often underwent early coronary angiography (86% vs. 66% vs. 47%, $p<0.001$) and PCI (42% vs. 21% vs. 15%, $p<0.001$). After adjustment for sex, bystander CPR, TTM and post-resuscitation shock, an early invasive strategy was associated with higher survival only in low-risk patients	Observational retrospective study Decision for early invasive strategy not standardised CAHP score alone may not be used for individual prediction. Lower number of patients and very low survival (3%) in the high risk group
Jakkula et al. [7]	Feasibility randomised clinical trial 2^3 factorial design Comatose patients resuscitated from witnessed OHCA with VF or VT Targeting low-normal or high-normal MAP Primary outcome serum concentration of NSE at 48 h	120 patients included in final analysis Clear separation in MAP between groups No significant difference in NSE values or any secondary outcomes between groups	Majority of patients from single centre Unblinded Intervention not started until ICU admission
Jakkula et al. [8]	Feasibility randomised clinical trial 2^3 factorial design Comatose patients resuscitated from witnessed OHCA with VF or VT Targeting low-normal (4.5–4.7 kPa) or high-normal (5.8–6.0 kPa) $PaCO_2$ and normoxia (PaO_2 10–15 kPa) or moderate hyperoxia (PaO_2 20–25 kPa)	120 patients included in final analysis Clear separation in $PaCO_2$ and PaO_2 between groups No significant difference in NSE values between groups High-normal $PaCO_2$ and moderate hyperoxia increased near-infrared spectroscopy (NIRS) values. No differences in any other secondary outcomes	Majority of patients from single centre Unblinded Intervention not started until ICU admission

Table 1 (continued)

Study	Aims and design	Findings	Limitations
Taccone et al. [10]	Observational study with retrospective analysis Convenience sample of post-cardiac arrest patients in ICU Aim to evaluate the correlation of non-invasively measured cerebral perfusion pressure (CPP) with cerebral oxygen saturation (rSO_2) and outcome CPP estimated using trans-cranial Doppler (TCD) to measure middle cerebral artery mean flow velocities (MFVmca) Estimated CPP (eCPP) = MAP × diastolic FVmca/MFVmca + 14	30 patients were evaluated Lower eCPP values in non-survivors compared with survivors; similar MFVmca, rSO_2 and MAP values between groups	Observational study using convenience sample TCD is operator dependent and acoustic window absent in 10–15% rSO_2 subject to extra-cerebral contamination and values reflect mainly venous saturation
Moseby-Knappe et al. [11]	Prognostic accuracy study Comatose patients resuscitated from OHCA of presumed cardiac origin Index test: neurofilament light chain (NFL) measured at 24, 48, ad 72 h after CA Prediction: poor neurological outcome (CPC 3–5) at 6 months	717 patients included NFL levels of 478 pg/mL at 24 h, 943 pg/mL at 48 h, and 963 pg/mL at 72 h had 98% specificity and 69–73% sensitivity for predicting poor outcome At all time points, AUROC was 0.94, greater than NSE, S-100B and tau protein At comparable specificities, NFL had greater sensitivity than SEPs, routine EEG, brain CT, and standard pupillary light reflex (s-PLR)	Very high levels (12,317 pg/mL at 24 h) were necessary to achieve 100% specificity, with consequent lower sensitivity (53%) Limited availability of the technique in routine laboratories Lack of external validation Need for established reference ranges
Oddo et al. [12]	Prognostic accuracy study Comatose patients resuscitated from cardiac arrest Index test: neurological pupil index (NPi) during the first 72 h after ICU admission Comparator: s-PLR Prediction: CPC 3–5 at 3 months	456 patients included Blinded NPi evaluation A NPi ≤ 2 predicted poor outcome with 100% specificity as early as 24 h from cardiac arrest NPi specificity was significantly higher than that of s-PLR	Inconsistent WLST policy (multicentre study) Low NPi specificity Potential interference of sedation on s-PLR results
Velly et al. [13]	Prognostic accuracy study Patients who were unresponsive at ≥ 7 days after cardiac arrest Index test: fractional anisotropy (WWM-FA) measured with MRI Derivation and validation cohorts Prediction: CPC 3–5 at 3 months	150 patients included in final analysis At 7–28 days after cardiac arrest, the AUROC for poor outcome of WWM-FA was 0.95 (091–0.98), significantly higher than that of standard MRI In the validation cohort, a WWM-FA < 0.91 had 100% specificity and 89.7 sensitivity for poor outcome	Complex technique Data were not interpretable in 25/185 (14%) eligible patients Not all comatose at the time of MRI (median GCS 9 [IQR 7–12] in patients with good outcome)

AED automatic external defibrillation, *HIBI* hypoxic-ischaemic brain injury, *AUROC* area under the receiver operating characteristic curve, *CPC* cerebral performance category, *GCS* Glasgow Coma Score, *ICU* intensive care unit, *IQR* interquartile range, *MAP* mean arterial pressure, *MRI* magnetic resonance imaging, *mRS* modified Rankin Scale score, *NSE* neuron-specific enolase, *OHCA* out-of-hospital cardiac arrest, $PaCO_2$ arterial carbon dioxide tension, PaO_2 arterial oxygen tension, *PCI* percutaneous coronary intervention, *SEPs* somatosensory evoked potentials, *STE* ST-segment elevation, *TTM* targeted temperature management, *VF/VT* ventricular fibrillation/ventricular tachycardia, *WLST* withdrawal of life-sustaining treatment

VF/VT OHCA. The investigators achieved clear separation in PaO_2, $PaCO_2$ and MAP between the groups but there was no difference in the values of neuron-specific enolase (NSE), a biomarker of HIBI, at 48 h after ROSC. High-normal $PaCO_2$ and moderate hyperoxia increased regional cerebral oxygenation (rSO_2) but there were no differences between the groups in any of the secondary outcomes.

One of several reasons for the failure to replicate the findings of previous observational studies is the likely considerable heterogeneity in optimal targets among patients. Approximately a third of post-CA patients will lose cerebral autoregulation and are likely to require a higher MAP to preserve cerebral blood flow [9]. rSO_2 has been used to determine optimal MAP in post-CA patients but it is unknown how well rSO_2 correlates with cerebral perfusion pressure (CPP). Taccone and colleagues have used trans-cranial Doppler to assess middle cerebral artery mean flow velocities (MFVmca) in 30 post-CA patients to provide an estimate of CPP (eCPP) [10]. Lower eCPP values were found in non-survivors compared with survivors, while MFVmca, rSO_2 and MAP values were similar between groups. It is possible that strategies to optimise eCPP instead of MAP or rSO_2 may improve neurological outcome.

Prognostication

Prediction of neurological outcome in comatose-resuscitated patients is challenging. Among indices for estimating severity of HIBI, NSE has several advantages: potential for blinded evaluation—therefore avoiding a self-fulfilling prophecy bias—and no influence from sedation and TTM. However, to obtain a specificity close to 100% for the prediction of poor outcome, very high levels are needed, and the consequent sensitivity is low. Moreover, NSE values are influenced by haemolysis [1].

In a substudy of the TTM trial [11], a new biomarker—neurofilament light chain (NFL)—was assessed blindly for neuroprognostication after CA. At 24 h, a NFL value of 478 pg/mL predicted poor neurological outcome at 6 months with 69 [57–79]% sensitivity and 98 [96–100]% specificity. The area under the receiver operating characteristic curve was 0.94 (0.92–0.95), greater than that of any other predictor, including NSE, brain CT, somatosensory evoked potentials, EEG, and clinical examination. Unlike NSE, NFL blood values are not influenced by haemolysis.

Clinical examination is crucial for neuroprognostication and absence of standard pupillary light reflex (sPLR) at ≥ 72 h is recommended as a robust predictor of poor neurological outcome after CA [1]. However, sPLR is operator dependent, qualitative and, since it cannot be concealed from the treating team, is prone to self-fulfilling prophecy bias. In a European 456-patient multicentre prognostication study [12] where the quantitative neurological pupil index (NPi) measured blindly using automated pupillometry was compared with sPLR, an NPi ≤ 2 during the first 72 h after ROSC had significantly higher specificity than an absent sPLR ($p < 0.001$). NPi predicted unfavourable outcome with 0% FPR as early as 24 h after CA. Among patients whose sPLR was scored as absent, those with false positives had a significantly smaller pupil size than those who had a poor neurological outcome (1.9 ± 0.22 vs. 2.8 ± 1.05 mm; $p = 0.009$), suggesting that miosis may have prevented clinicians from detecting sPLR.

Neuroprognostication guidelines focus on the early post-resuscitation phase (72–96 h), while little is known about late predictors. In a multicentre prognostication study [13], fractional anisotropy (WWM-FA) measured on magnetic resonance imaging (MRI) was evaluated as a predictor of poor neurological outcome at 6 months in post-ROSC patients who had been unconscious for at least 7 days. A WWM-FA threshold of 0.91 was identified in a 150-patient derivation cohort as a prediction and subsequently tested in a 50-patient validation cohort, where it showed 89.7 (75.8–97.1) % sensitivity and 100 (69.1–100) % specificity for prediction of poor outcome. Despite its complex measurement, WWM-FA is a promising predictor in late awakeners after CA.

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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