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LESS IS MORE IN ICU

Vasopressors, antiarrhythmics, oxygen, and intubation in out-of-hospital cardiac arrest: possibly less is more

Claudio Sandroni[1*], Markus B. Skrifvars[2] and Jasmeet Soar[3]

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Out-of-hospital cardiac arrest (OHCA) is a major cause of death in Western countries [1]. While bystander cardiopulmonary resuscitation (CPR) and early defibrillation are associated with improved outcomes, the impact of advanced life support (ALS) is less clear [2]. Recently, a series of randomised controlled trials assessed the effect of major ALS interventions: tracheal intubation, vasopressor and antiarrhythmic drugs during CPR, and oxygenation, ventilation and hemodynamic management strategies after return of spontaneous circulation (ROSC).

The rationale for the use of epinephrine (adrenaline) in CA is to increase diastolic pressure, coronary blood flow and myocardial perfusion during CPR [3]. Indirect evidence from an unblinded trial [4] in 2009 and from large retrospective observational studies [5, 6] suggested that epinephrine improved ROSC but not survival to hospital discharge. Moreover, there was concern about a potential association between epinephrine and worse neurological outcome in survivors. Both these hypotheses were investigated by the recent PARAMEDIC-2 trial [7] that randomised 8014 adults with OHCA to epinephrine or placebo. Epinephrine was associated with significantly higher 30-day survival (odds ratio [OR] 1.39; 95% confidence interval [CI] 1.06–1.82) and higher albeit non-significant rates of survival with good neurological outcome (OR 1.18 [0.86–1.61]), but with higher rates of severe neurologic impairment among survivors in the epinephrine group (31% vs. 18%). It should be noted that—as often occurs in interventional studies on OHCA—the rates of the primary outcome (survival to hospital discharge) were lower than expected, which significantly reduced the power of the trial.

In CA with shock-refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT), antiarrhythmics (amiodarone or lidocaine) are recommended to improve the chances of successful defibrillation. In 2016, the North-American ALPS trial [8] randomised 3026 OHCAs with shock-refractory VF/pVT to amiodarone 300 mg, lidocaine 120 mg, or placebo. In per-protocol analysis, the ROSC rates were significantly higher with lidocaine (350/974 [39.9%]) versus placebo (366/1059 [34.6%]; difference 5.4 [1.2–9.5]). Overall survival to hospital discharge did not differ between groups but, in patients with a witnessed arrest, It was significantly higher with both amiodarone and lidocaine than with placebo (27.7% and 27.8% vs. 22.7%; difference 5.0% [0.3–9.7%] and 5.2% [0.5–9.9%], respectively). The trial was potentially underpowered for the primary endpoint. Other limitations included a late administration of study drugs and the use of a non-standard preparation of amiodarone (see Table 1).

Three recent randomised trials of airway interventions during CPR in patients with OHCA have challenged

*Correspondence: claudio.sandroni@policlinicogemelli.it
[1] Istituto Anestesiologia e Rianimazione, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario "Agostino Gemelli" - IRCCS, Largo Francesco Vito, 1, 00168 Rome, Italy
Full author information is available at the end of the article

Table 1 Evidence from recent trials on ALS and post-cardiac arrest interventions

Study	Aims and design	Findings	Limitations
PARAMEDIC2 Perkins [6] (ISRCTN73485024)	To assess effectiveness and safety of parenteral epinephrine in OHCA Intravenous or intraosseous route Adult patients with OHCA (all rhythms) resuscitated by paramedics Randomised, placebo-controlled trial at five NHS ambulance services in UK Primary endpoint: survival at 30 days Secondary endpoint: survival with good neurological outcome, defined as a mRS ≤ 3, blindly assessed at 30 and 90 days	ROSC rates three times higher with epinephrine (1457/4015 [36.3%] vs. 468/3999 [11.7]) 30-day survival more common with epinephrine $n=130/4012$ (3.2%), placebo $n=94/3995$ (2.4%); adjusted OR 1.47 [1.09–1.97] More 30-day survivors with good neurological outcome with epinephrine $n=87/4007$ (2.2%); placebo $n=74/3994$ (1.9%), adjusted OR 1.19 (0.85–1.68) Severe neurologic impairment more common in survivors in the epinephrine group (39/126 [31.0%] vs. 16/90 [17.8%] No evidence of modification in treatment effect by witnessed status, bystander CPR, initial rhythm or time to agent administration	Survival rates much lower than anticipated Insufficient power to detect significant effects in secondary outcomes Little information about CPR quality (fewer than 5% of patients and only about the first 5 min of arrest)
ALPS Kudechuck [7] (NCT01401647)	To compare parenteral amiodarone (300 mg repeated once at 150 mg if needed), lidocaine (120 mg repeated once at 60 mg if needed), and placebo for shock-refractory VF/pVT Intravenous or intraosseous route Adult patients with OHCA with VF/pVT after ≥ 1 shock resuscitated by paramedics Randomised, placebo-controlled trial at 10 sites in North America Primary endpoint survival at discharge Secondary endpoint: survival at discharge with good neurological outcome (mRS ≤ 3)	Good CPR quality, in terms of chest compression rate, depth, and compression fraction Higher ROSC rates for lidocaine (396/992 [39.9%]) versus amiodarone (350/974 [35.9%]) versus placebo (366/1059 [34.6%]). Significant difference for lidocaine versus placebo (5.4% [1.2–9.5]) No significant difference in survival at discharge in the overall population (237/970 [24.4] vs. 233/985 [23.7] vs. 222/1056 [21.0] for amiodarone, lidocaine and placebo, respectively) In witnessed arrests, significantly higher rates of survival to discharge with both amiodarone and lidocaine versus placebo (difference 5.0% [0.3–9.7%] and 5.2% [0.5–9.9%], respectively) No difference in secondary outcomes	Potentially underpowered (the point estimates of primary outcome differed less than anticipated) Time to study drug 19 min in all three study groups Potential interference from administration route (significantly higher rates of survival to discharge with intravenous, but not intraosseous amiodarone) Use of a non-standard, Captisol-based formulation of amiodarone
AIRWAYS-2 Benger [8] (ISRCTN08256118)	Cluster randomised controlled trial of i-gel supraglottic airway (SGA) device versus tracheal intubation in the initial airway management of out-of-hospital cardiac arrest Setting—UK Paramedics randomised to use i-gel or tracheal intubation strategy for initial advanced airway Primary endpoint: neurological outcome at hospital discharge or at 30 days if still hospitalised	9296 patients enrolled 311/4882 SGA patients (6.4%) versus 300/4407 patients (6.8%) had a good neurological outcome at discharge—there was no risk adjusted difference between groups Higher ventilation success rate with SGA (87.4% vs. 79.0%) Similar regurgitation and aspiration reported with SGA (26.1% vs. 24.5%)	Randomised according to paramedic and looked at an airway strategy as opposed to device Intervention could not be blinded Not all patients got an advanced airway, and SGA insertion was more likely than tracheal intubation Tracheal intubation success rate reported as 69.8% Crossover between groups Results are not generalizable to other systems of care or different SGA devices
CAAM Jabre [9] (NCT02327026)	Multicentre randomised controlled trial comparing bag-mask ventilation (BMV) with tracheal intubation in patients with out-of-hospital cardiac arrest Setting—France and Belgium Physician based system Primary outcome: 28-day survival with favourable neurological outcome	2043 patients were randomised High intubation success rate: 97.9%. Favourable functional survival at day 28 was 44 of 1018 patients (4.3%) in the BMV group and 43 of 1022 patients (4.2%) in the tracheal intubation group (difference, 0.11% [one-sided 97.5% CI -1.64% to ∞]; p for noninferiority $=0.11$). Complications in the BMV group versus intubation: difficult airway management (186/1027 [18.1%] vs. 134/996 [13.4%]; $p=0.004$), failure (69/1028 [6.7%] vs. 21/996 [2.1%]; $p<0.001$) Regurgitation of gastric content (156/1027 [15.2%] vs. 75/999 [7.5%]; $p<0.001$)	Study design gave an inconclusive result. Probably underpowered Intervention could not be blinded Results cannot be extrapolated to different systems Cross-over for those patients where BMV was difficult

Table 1 (continued)

Study	Aims and design	Findings	Limitations
PART Wang [10] (NCT02419573)	Cluster randomised trial comparing tracheal intubation and laryngeal tube (LT) insertion in out-of-hospital cardiac arrest Setting—North America Emergency medical technician-based system. Primary outcome: 72-h survival	3000 patients in primary analysis Initial airway success 90.3% with LT, 51.6% with intubation 72 h survival 18.3% in LT versus 15.4%; $p=0.04$) Secondary outcomes in the LT group versus intubation: ROSC (27.9% vs. 24.3%; $p=0.03$) Hospital survival (10.8% vs. 8.1%; $p=0.01$) Favourable neurological status at discharge (7.1% vs. 5.0%; $p=0.02$)	Low tracheal intubation success rates limits generalizability of findings to other systems Intervention could not be blinded Only funded and powered for primary 72-h endpoint
COMACARE Jakkula [13, 14] (NCT02698917)	To compare targeting high or low PaO_2 (20–25 vs. 10–15 kPa), $PaCO_2$ (5.8–6.0 vs. 4.5–4.7 kPa) and MAP (65–75 vs. 80–100 mmHg) during the first 36 h in adults resuscitated from OHCA with VF as the initial rhythm and treated with TTM Targets were achieved with different fractions of inspired oxygen, minute ventilation and doses of norepinephrine 120 patients treated at five centres in Finland and one in Denmark Primary endpoint: NSE levels at 48 h	Treatment goals were achieved well No difference in NSE levels between groups: median 20.6 [IQR 14.2–34.9] µg/l in high-oxygen group versus 22.3 [14.8–27.8] µg/l in normal group median 22.5 [14.2–34.9] µg/l in high-$PaCO_2$ group versus 18.8 [13.9–28.3] µg/l in low group median 22.0 [13.6–30.9] µg/l in high-MAP group versus 20.6 [15.2–34.9] µg/L in low group) Higher oxygen and carbon dioxide improved brain oxygenation by NIRS	Pilot trial, underpowered to show difference in patient outcome Intervention could not be blinded NSE has been criticised to be a suboptimal brain injury marker due to haemolysis among other
NEUROPROTECT Ameloot [16] (NCT02541591)	To compare an early goal directed haemodynamic optimization strategy (MAP 85–100 mmHg, SVO_2 65–75%) with a MAP 65 mmHg strategy for reducing HIBI in adult survivors of OHCA (all rhythms) of a presumed cardiac cause Hemodynamic targets were achieved with norepinephrine, fluids, inotropes and packed RBCs, following a predefined flowchart in the intervention arm, or at the discretion of the treating physician in the control arm Setting—single centre in Belgium Primary outcome was the extent of HIBI as quantified by the apparent diffusion coefficient (ADC) on DW-MRI Main secondary outcome: favourable neurological outcome at ICU discharge and at 6 months	112 patients treated Cerebral oxygenation was higher in the hemodynamic optimization group The percentage of voxels below an ADC score of 650.10–6 mm^2/s on diffusion-weighted MRI did not differ between groups (median 16% vs. 12%, OR 1.37[0.95–1.98]; $p=0.09$]) No difference in neurological outcome at ICU discharge or 6 months Less predefined severe adverse events in the hemodynamic optimization group (3% vs. 33%, OR 0.32 [0.12–0.85]; $p=0.02$)	Unclear clinical relevance of the diffusion-weighted MRI used as the main endpoint Intervention could not be blinded Potentially underpowered

CPR cardiopulmonary resuscitation, *DW-MRI* diffusion-weighted magnetic resonance imaging, *HIBI* hypoxic–ischaemic brain injury, *ICU* intensive care unit, *MAP* mean arterial pressure, *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, *RBCs* red blood cells, *VF/pVT* ventricular fibrillation/pulseless ventricular tachycardia

whether tracheal intubation increases ROSC and neurologically intact survival compared with bag-mask ventilation or a supraglottic airway device (Table 1) [9–11]. Jabre and colleagues reported no difference in 28-day survival with favourable neurological outcome in 2040 patients between bag-mask ventilation and tracheal intubation by experienced prehospital physicians (RR 1.03; 95% CI 0.68–1.55) [10]. The overall success rate of tracheal intubation was high (98%). There were significantly more difficulties in airway management (18.1% vs. 13.4%) and regurgitation of stomach contents (15.2% vs. 7.5%) in the bag-mask group. Benger and colleagues compared the use of the i-gel supraglottic airway with tracheal intubation by paramedics in 9289 patients with OHCA [9]. This study showed no difference in survival to hospital discharge with favourable neurological outcome (RR 0.92; 95% CI 0.77–1.09) and reported a tracheal intubation success rate of 69.8%. Finally, the study by Wang and colleagues compared the use of the laryngeal tube with tracheal intubation by emergency medical technicians in 2999 patients. They reported an increased survival to hospital with favourable neurological outcome with the laryngeal tube (RR 1.42; 95% CI 1.07–1.89) [11]. Importantly tracheal intubation success rate was only

52% in this study. These three RCTs highlight the difficulties of studying airways in OHCA patients. In addition to requiring adequate power, patients who get early CPR and have the best outcomes might not need an advanced airway, most patients get more than one airway intervention, rescuers can choose to switch between airway techniques, and success varies according to rescuer skills and patient factors. The studies suggest that tracheal intubation should only be used in settings with a high success rate. The evidence appears to support a "less is more" approach to airway management during CPR. The airway used will depend on patient factors and rescuer skills, and aim to use the least invasive airway strategy that enables effective oxygenation and ventilation during CPR.

In patients with ROSC, hypoxic–ischaemic brain injury (HIBI) is the main cause of morbidity and mortality including decreased cerebral perfusion resulting in ischemia [12, 13]. Two recent studies of physiological targets during intensive care provide preliminary on the effect of aiming to improve brain oxygenation during post-cardiac arrest care. The COMACARE [14, 15] was a factorial pilot study randomising 120 patients to high-normal versus low-normal targets of arterial oxygen (PaO_2), carbon dioxide ($PaCO_2$) and mean arterial blood pressure (MAP). The primary endpoint was plasma neuron-specific enolase (NSE) level, a marker for HIBI [16] Regional brain oxygenation (rSO_2) was a secondary endpoint. The NEUROPROTECT trial [17] randomised 110 OHCA survivors to early goal-directed haemodynamic optimization (targeting MAP between 85 mmHg and 100 mmHg and SVO_2 between 65%, and 75%) versus a MAP 65 mmHg strategy. Targets were maintained for 36 h from ICU admission using fluids, vasopressors and inotropes (according to a predefined protocol in the intervention arm, and at discretion of the treating physician in the control arm). The COMACARE study showed significantly improved rSO_2 with targeting PaO_2 of 20–25 kPa and $PaCO_2$ of 6 kPa; however, this did not result in any decrease in NSE. Similarly, the NEUROPROTECT study showed an improvement of brain oxygenation with hemodynamic optimisation but without any difference in neurological injury assessed with magnetic resonance imaging.

In conclusion, recent trials have challenged the role of advanced interventions for CA. Antiarrhythmics and vasopressors increase short-term survival but this should be balanced against the risk of futility and an increased number of survivors with severe HIBI. Targeted ventilation and haemodynamic strategies increase brain oxygenation, but without any beneficial effect on surrogate markers of HIBI. It appears less may be more when it comes to many commonly used advanced interventions during CPR and after ROSC—future research needs to give us a better understanding of the circumstances when these interventions improve patient outcomes.

Author details
[1] Istituto Anestesiologia e Rianimazione, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario "Agostino Gemelli" - IRCCS, Largo Francesco Vito, 1, 00168 Rome, Italy. [2] Department of Emergency Medicine and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [3] Intensive Care Unit, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB, UK.

Compliance with ethical standards

Conflicts of interest
Dr. Skrifvars reports personal fees from Bard Medical Ireland, personal fees from INVOS Covidien, unrelated to the submitted work; he is also the PI of the COMACARE study that is discussed in the current review. Dr. C. Sandroni has no conflicts of interest to disclose. Dr. J. Soar reports he was a steering committee member for the AIRWAYS-2 study, and a member of the data monitoring committee for the PARAMEDIC2 Trial.

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