Early neuroprotection after cardiac arrest

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Purpose of review
Many efforts have been made in the last decades to improve outcome in patients who are successfully resuscitated from sudden cardiac arrest. Despite some advances, postanoxic encephalopathy remains the most common cause of death among those patients and several investigations have focused on early neuroprotection in this setting.

Recent findings
Therapeutic hypothermia is the only strategy able to provide effective neuroprotection in clinical practice. Experimental studies showed that therapeutic hypothermia was even more effective when it was started immediately after the ischemic event. In human studies, the use of prehospital hypothermia was able to reduce the time to target temperature but did not result in higher survival rate or neurological recovery in patients with out-of-hospital cardiac arrest, when compared with standard in-hospital therapeutic hypothermia. Thus, intra-arrest hypothermia (i.e., initiated during cardiopulmonary resuscitation) may be a valid alternative to improve the effectiveness of therapeutic hypothermia in this setting; however, more clinical data are needed to demonstrate any potential benefit of such intervention on neurological outcome. Together with cooling, early hemodynamic optimization should be considered to improve cerebral perfusion in cardiac arrest patients and minimize any secondary brain injury. Nevertheless, only scarce data are available on the impact of early hemodynamic optimization on the development of organ dysfunction and neurological recovery in such patients. Some new protective strategies, including inhaled gases (i.e., xenon, argon, nitric oxide) and intravenous drugs (i.e., erythropoietin) are emerging in experimental studies as promising tools to improve neuroprotection, especially when combined with therapeutic hypothermia.

Summary
Early cooling may contribute to enhance neuroprotection after cardiac arrest. Hemodynamic optimization is mandatory to avoid cerebral hypoperfusion in this setting. The combination of such interventions with other promising neuroprotective strategies should be evaluated in future large clinical studies.

Keywords
cardiac arrest, hemodynamic optimization, intra-arrest hypothermia, neuroprotection, prehospital hypothermia

INTRODUCTION

Cardiac arrest is a major cause of morbidity and mortality in western countries. About 350 000 persons in the United States [1] and approximately 275 000 in Europe [2] experience out-of-hospital cardiac arrest (OHCA) annually [1,2]. However, over the past decades, long-term survival and neurological outcomes have been significantly improved through the implementation of an integrated system of care focusing on standardized emergency response and the development of postresuscitation care bundles [3,4].

Only few interventions have demonstrated to improve the rate of return of spontaneous circulation (ROSC) and long-term outcome after cardiac arrest, including early and appropriate cardiopulmonary resuscitation (CPR), bystander CPR, early defibrillation for shockable rhythms, and the use of therapeutic hypothermia [5,6]. Indeed, two pivotal randomized clinical trials (RCTs) showed that therapeutic hypothermia was associated with a better neurological function in comatose survivors from OHCA with a shockable rhythm [7,8]; nevertheless, a recent RCT questioned the optimal target temperature in these patients and

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KEY POINTS

- Early therapeutic hypothermia can reduce the time to target temperature but did not result in higher survival rate or neurological recovery in patients with out-of-hospital cardiac arrest, when compared with standard inhospital therapeutic hypothermia.
- Intra-arrest hypothermia (i.e., initiated during cardiopulmonary resuscitation) may be a valid alternative to improve the effectiveness of therapeutic hypothermia in this setting; however, more clinical data are needed.
- Early hemodynamic optimization should be considered to improve cerebral perfusion in cardiac arrest patients and minimize any secondary brain injury.
- New protective strategies, including inhaled gases (i.e., xenon, argon, nitric oxide) and intravenous drugs (i.e., erythropoietin) are emerging in experimental studies as promising tools to improve neuroprotection, especially when combined with therapeutic hypothermia.

underlined the need to better understand how to manage and improve the benefits of therapeutic hypothermia in this setting, such as the time to initiate therapeutic hypothermia and the target population [9▪▪]. Moreover, postanoxic encephalopathy has a complex and multifactorial pathophysiology (Fig. 1). The mitigation of postanoxic injury also requires the development of other treatments that, in combination with cooling, may be more effective to improve neurologic recovery. Although multiple drug treatments explored so far have failed to show such benefits in cardiac arrest patients [10,11], a recent rising interest has been directed toward new therapeutic strategies that may provide additional neuroprotection in this setting.

The aim of this review was to describe the early available therapies that can effectively ameliorate outcome in comatose survivors from cardiac arrest, including new evidence on the use of therapeutic hypothermia (either prehospital or intra-arrest), on the rapid hemodynamic optimization and on some new promising treatments that might be available for widespread use in the next years.

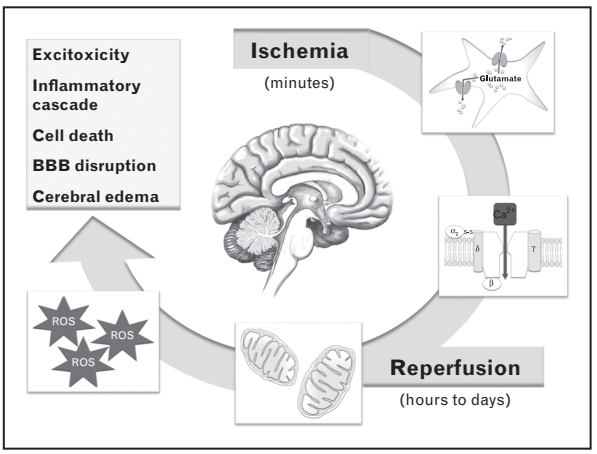

FIGURE 1. Summary of main mechanisms implicated in the postanoxic brain injury. BBB, brain–blood barrier; ROS, reactive oxygen species.

EARLY COOLING

Therapeutic hypothermia provides effective neuroprotection by increasing tissue tolerance to ischemia, on one hand, and by hampering the development of inflammatory cascade and radical oxygen species (ROS) production after reperfusion, on the other (Fig. 2) [12,13]. Experimental studies yielded that therapeutic hypothermia was even more effective when it was initiated immediately after the ischemic event [14▪]. Kuboyama *et al.* [15] showed that in a canine model of cardiac arrest, therapeutic hypothermia induced after reperfusion improved cerebral functional and reduced histological damage, whereas a delay of 15 min in cooling administration had no beneficial effects on brain recovery. The effects of cooling on brain injury were further enhanced if hypothermia could be implemented before the cerebral insult; in this setting, many data from patients undergoing cardiac surgery or from experimental focal cerebral ischemia have already shown the great benefits of preinjury cooling in preserving neurocognitive

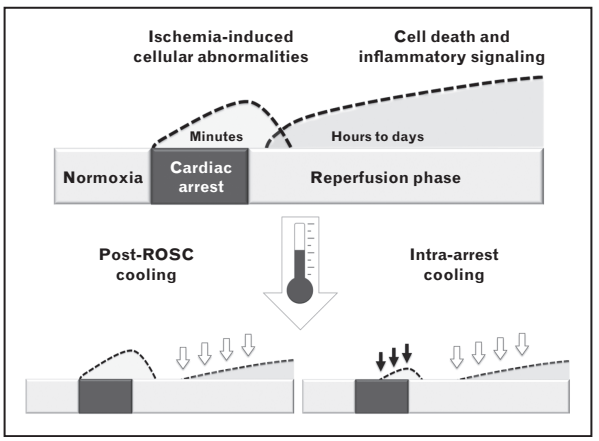

FIGURE 2. The effects of cooling on ischemia and reperfusion injury, with regard to initiation after the return of spontaneous circulation or during cardiopulmonary resuscitation. White arrows indicate the effects of cooling initiated after ROSC on the reperfusion injury. Black arrows indicate the additional effects of intra-arrest hypothermia on the ischemic injury occurring during arrest.

function or minimizing the extent of the infarct size [16,17]. Unfortunately, this strategy cannot be implemented in patients suffering from cardiac arrest, as this cannot be foreknown. Thus, the best way to minimize time from cerebral injury to therapeutic hypothermia is to cool patients as soon as possible when cardiac arrest occurs, that is, either during CPR or immediately after ROSC (Table 1) [18–20,21▪▪,22▪▪,23].

Prehospital hypothermia

A rapid and cheap method to initiate hypothermia immediately after ROSC and in an out-of-hospital setting is the infusion of cold fluids during a short period of time. Some feasibility studies yielded no major complications in patients who received such treatment and most of them suggested the administration of 30 ml/kg of crystalloids over 30 min to achieve around 1.5°C temperature reduction before hospital admission [18,19,24]. Also, Skulec *et al.* [25] suggested that a lower liquid amount (15–20 ml/kg) could be effective as well. Moreover, this strategy allowed a more rapid achievement of target temperature in prehospital cooled patients when compared with those treated with hypothermia after hospital admission [20].

However, Diao *et al.* [26] reviewed the available literature on this topic and collected in a meta-analysis all the RCTs evaluating the role of prehospital hypothermia on outcome of cardiac arrest patients. Five studies [18–20,21▪▪,23], including a total of 633 patients, were eventually selected. Although the analysis was biased because one study initiated therapeutic hypothermia during CPR and not after ROSC [23], prehospital cooling was more effective in reducing core temperature [mean overall difference −0.95°C (95% CI, confidence interval, −1.15 to −0.75)] than standard hypothermia but showed no significant benefit on survival and good neurological outcome [risk ratio for favorable outcome 1.01 (95% CI 0.82–1.25)]. Even when patients were considered separately according to their initial rhythm, no differences emerged and only one study suggested a trend toward a better outcome in patients receiving prehospital hypothermia with a shockable rhythm when compared with standard in-hospital cooling [18].

The question whether early cooling may be beneficial has become even more controversial after some recent retrospective studies showed that those patients who achieved more rapidly the target temperature after cardiac arrest had no major differences in overall neurological outcome when compared with the others [27] or presented an even higher risk of increased mortality [28,29▪]. This

Table 1. Summary of main studies dealing with early therapeutic hypothermia after cardiac arrest

Author	Type of study	Intervention	Number of patients (treatment/control)	TTM (hours) treatment versus control	Complications treatment versus control	Survival treatment versus control	Neurological outcome (CPC 1-2) treatment versus control
Kim [18]	RCT	PHC – cold fluids	125 (63/62)	NA	ReCA (24 versus 21%) PE (44 versus 55%)	33 versus 29%	33 versus 27.4%
Kamarainen [19]	RCT	PHC – cold fluids	43 (23/20)	NA	ReCA (10.5 versus 17%) PE (none)	35 versus 40%	35 versus 40%
Bernard [20]	RCT	PHC – cold fluids	234 (118/116)	NA	NA	48 versus 53%	48 versus 53%
Bernard [21▪▪]	RCT	PHC – cold fluids	163 (82/81)	NA	NA	13 versus 9%	12 versus 9%
Kim [22▪▪]	RCT	PHC – cold fluids	1359 (688/671)	4.2 versus 5.5	ReCA (26 versus 21%)* PE (41 versus 30%)**	38 versus 37%	33 versus 34%
Castren [23]	RCT	IATH – TNEC	200 (96/104)	1.7 versus 4.8	ReCA (3 versus 2%) -	44 versus 31%	34 versus 21%

CPC, Cerebral Performance Category; IATH, intra-arrest therapeutic hypothermia; PE, pulmonary edema; PHC, prehospital cooling; RCT, randomized clinical trial; ReCA, rearrest; TNEC, transnasal evaporative cooling; TTM, time to target temperature.
*$P = 0.008$.
**$P < 0.01$.

was in contrast with the results published by Wolff *et al.* [30], who showed that a delay in reaching target temperature was independently associated with a worse outcome [OR (odds ratio) for every hour 0.69 (95% CI 0.51–0.98)] in a prospective cohort of 49 comatose cardiac arrest patients. Interestingly, in this study patients were cooled by a closed-loop endovascular system and not by cold fluids, as in the other studies. It remains thus still unclear whether cold fluids, which may potentially reduce the coronary perfusion pressure and more slowly provide brain cooling than other techniques [29▪,31], could be considered as the optimal cooling strategy to implement prehospital hypothermia in this setting.

In order to better define the impact of early cooling, Kim *et al.* [22▪▪] have recently published a large RCT, which aimed to assess the effectiveness and usefulness of prehospital therapeutic hypothermia in comatose survivors from cardiac arrest. Over a 5-year period, the authors randomized 1359 OHCA (583 with ventricular fibrillation and 776 without ventricular fibrillation) to receive either early post-ROSC cooling with 2 l of intravenous saline or standard treatment. A significant reduction in mean core temperature by −1.20°C (95% CI −1.33 to −1.07°C) in patients with ventricular fibrillation and by −1.30°C (95% CI −1.40 to −1.20°C) in patients without ventricular fibrillation was observed. However, survival was similar between the two groups, both for patients with ventricular fibrillation (62.7 versus 64.3%, $P = 0.69$) and those without ventricular fibrillation (19.2 versus 16.3%, $P = 0.30$). Furthermore, rearrest, diagnosis of pulmonary edema, and diuretics requirement were significantly more frequent in the prehospital therapeutic hypothermia group, suggesting a potentially detrimental role for cold fluids in this setting.

The study by Kim *et al.* [22▪▪] offers some interesting insights into rapid cooling after cardiac arrest and points out some limitations of fluid administration in this setting. First, nearly 65% of the whole studied population received in-hospital cooling and only 60% actually reached goal temperature; thus, if an early prehospital cooling strategy could have been effective in reducing the postanoxic injury, these benefits were lost in one-third of the patients who were not kept within therapeutic temperature ranges thereafter. Second, although prehospital cooled patients reached target temperature earlier than others (4.2 versus 5.5 h, $P < 0.001$), this difference of only 1 h between groups might have been too small to expect an improvement in survival rate and neurological recovery. Third, the use of saline solutions could be questionable because of well known detrimental side effects of chloride-rich solutions, such as increased metabolic acidosis or cellular edema [32]. Finally, no studies on prehospital cooling have provided consistent hemodynamic monitoring data so far, hampering the evaluation of the real hemodynamic impact of fluids on these patients, especially on those with underlying moderate to severe heart disease.

Importantly, in the pivotal articles that introduced therapeutic hypothermia after cardiac arrest in clinical practice, time to hypothermia has also been quite variable among studies, ranging from 2 [7] to 8 h [8]. However, the 'therapeutic window' for initiating therapeutic hypothermia (i.e., the time after arrest during which therapeutic hypothermia is most effective) is narrow, and it is possible that only ultrafast cooling may improve postresuscitative neurologic outcome when compared with cooling initiated within 4–8 h after arrest. Unfortunately, this hypothesis has not been specifically studied and needs to be evaluated in future RCTs.

Intra-arrest hypothermia

Considering the pitfalls of studies dealing with prehospital therapeutic hypothermia, more interest has been directed toward intra-arrest hypothermia (IATH). Many animal data provided convincing evidence that IATH was effective in improving ROSC rates and also defibrillation success, resulting in a better recovery of left ventricular ejection fraction [33–35]. A recent publication systematically reviewed all experimental and clinical studies dealing with IATH after cardiac arrest [14▪]. Despite some positive effects on cardiac function, animal studies yielded conflicting results regarding mortality, because only in a minority of cases higher survival rates were showed in animals treated with IATH. Nevertheless, almost all animal findings agree to confirm a better neurological performance in the IATH group compared with both normothermia and post-ROSC hypothermia. This effect has been attributed to improved preservation of cerebral function through inhibition of glutamate release [36], to the attenuation of the alterations of the blood brain barrier [37] and to the decrease in intracranial pressure and increase in cerebral blood flow [38]. Many limitations of animal studies hamper understanding of the real benefit brought by IATH. Indeed, animal models are quite far from real life, because cardiac arrest time is shorter, observation period after cardiac arrest is generally brief and different animal sizes affect significantly time to reach target temperature (i.e., very short for small animals, such as rodents) and mode of cooling.

In humans, the simplest way to start IATH is by cold liquid infusion, but maybe this is not also the safest [30]; however, most of the other available

techniques, including surface blankets/pads or intravascular catheters need an energy supply and cannot be used outside the hospital. Considering the promising results of animal trials, some investigators tried to assess the feasibility and effectiveness of IATH in the human setting. Indeed, Bruel *et al.* [39] investigated feasibility of intra-arrest cooling by cold saline infusion in 33 patients after OHCA, showing a huge decrease in core temperature of treated patients (−2.1°C at the end of infusion) with a median time to target temperature (34°C) of 16 min (IQR 11.5–25.0 min) after ROSC; one episode of pulmonary edema was reported. Thereafter, Kamarainen *et al.* [40] cooled 17 OHCA patients with cold saline during CPR, obtaining a decrease in core temperature at hospital arrival of −1.3°C, with a mean volume infused of 1571(±517) ml. Five patients experimented hypotension and only one survived to hospital discharge. Finally, Garret *et al.* [41], in a retrospective cohort of 551 patients, reported an increased ROSC rate and hospital admission for patients receiving IATH using cold fluids infusion, without any differences in other outcome variables (i.e., mortality and neurological recovery). Interestingly, the authors also found a direct correlation between the amount of liquid infused and the occurrence of ROSC and explained this finding as a hypothetical 'selective cardiac cooling' starting from the first milliliters of liquid infused, which protected the myocardium during the ischemic injury. However, this correlation might also be due to some differences in the quality of CPR that affected directly the velocity of liquid infusion in a cardiac arrest scenario [42] and, more importantly, the percentage of patients achieving ROSC [43,44]. Also, only the subgroups of patients with pulseless activity/asystole had a significant improvement in outcome when treated with IATH and determined the overall result. Finally, it is possible that an increased occurrence of noncardiac causes of cardiac arrest, such as underlying infectious disease [45], may have explained the benefits of such strategy, as these conditions are particularly sensitive to fluid administration.

The main limitation of cold infusions is that the brain can be cooled very poorly before reperfusion. In one study, Callaway *et al.* [46] investigated the effects of direct cranial cooling during CPR with ice packs placed on patients' head and neck. More treated patients achieved ROSC (33 versus 0%), even if core temperature was not different between groups on hospital admission (−0.04 ± 0.07°C). Unfortunately, all patients died afterward, making it impossible to draw any conclusion on the potential benefits of such strategy. A valid and effective alternative to cranial cooling to induce selective head hypothermia is the use of transnasal evaporative cooling (TNEC); this strategy has been shown to provide brain cooling in experimental cardiac arrest, even in the absence of spontaneous circulation without major side effects, and to improve success of resuscitation [47]. In 84 patients with postanoxic coma, TNEC used for 1 h was demonstrated to be feasible and to be effective in reducing tympanic temperature by a median of 2.3°C in the hospital setting [48]. In the only human RCT in the field of IATH [25], Castren *et al.* [23] randomized patients to receive either standard treatment with inhospital therapeutic hypothermia or to the use of a TNEC device during CPR. Among the 200 enrolled patients, 104 received standard therapy and 96 IATH, with the last ones having a significantly lower temperature at hospital admission (34.2 ± 1.5°C versus 35.5 ± 0.9°C, $P < 0.001$) and a lower time to target temperature (284 versus 155 min, respectively, $P < 0.01$). However, IATH did not result in any improvement in survival rate or good neurological outcome; only in the subgroup of patients with a time from collapse to CPR below 10 min, IATH was associated with higher rate of survivors and of good neurological recovery (56.5 versus 29.4%, $P = 0.04$; 43.5 versus 17.6%, $P = 0.03$, respectively). Few nonsevere adverse events associated with IATH were nasal bleeding or frozen nose. Considering that this study was not specifically designed to show any improvement on outcome, a new RCT is actually ongoing, using the same investigational design, to demonstrate any potential benefit from transnasal cooling during CPR on the outcome of patients after cardiac arrest [49].

EARLY HEMODYNAMIC OPTIMIZATION

After ROSC and hospital admission, many survivors from cardiac arrest develop a systemic hemodynamic impairment that may induce cerebral hypoperfusion, if it is not promptly corrected. This so-called postcardiac arrest syndrome (PCAS) [50] shares several pathophysiological mechanisms with sepsis and may contribute both to burden brain damage and to impair cardiac and/or respiratory functions, eventually leading to multiorgan failure (MOF) [51]. In order to improve hemodynamics after cardiac arrest, it is mandatory to identify and treat all the possible reversible causes of cardiovascular impairment, including cardiac tamponade, pulmonary embolism, tension pneumothorax, and distributive shock (anaphylactic or septic) [52]; also, in the case of suspected myocardial infarction, coronary angiography should be rapidly performed to treat any critical stenosis, especially in the case of shockable rhythms [53].

Surprisingly, despite the obvious importance of this issue, we have scarce data on the role of hemodynamic optimization after cardiac arrest. Moreover, a recent review of the literature was unable to retrieve any article dealing with this topic in comatose postanoxic patients [54]. In 2009, Gaieski *et al.* [55] published a study in which they evaluated the effects on survival of a therapeutic protocol including early goal-directed hemodynamic optimization (EGDHO) and the use of therapeutic hypothermia. Over a 2.5-year period, the authors enrolled 20 patients who were eventually matched with 18 historical controls, undergoing standard therapy. In the EGDHO group, patients were cooled immediately after ROSC with cold fluids and then systemic hemodynamics were optimized following a predefined algorithm that aimed at mean arterial pressure (MAP) between 80 and 100 mmHg; central venous pressure (CVP) between 8 and 20 mmHg; central venous saturation ($S_{cv}O_2$) greater than 65%. Treated patients received many more fluids and had a higher fluid balance after 24 h from admission (+5566 versus +1352 ml, respectively); they also received more frequently inotropes (29 versus 0% after 1 h; 39 versus 0% after 6 h; 33 versus 0% after 24 h) than historical controls. A trend toward a reduction in mortality, from 78% in the control group to 50% in the intervention group ($P = 0.15$) was found. A quite similar therapeutic protocol was used by Walters *et al.* [56]; in a prospective study, in which the hemodynamic optimization included MAP greater than 65 mmHg, CVP greater than 12 mmHg and $S_{cv}O_2$ greater than 70%, 29 patients treated with this approach were compared with 26 historical matched controls receiving standard therapy; the bundle of therapy included also the use of therapeutic hypothermia. Mortality was not significantly different (bundle 55% versus controls 69%, $P = 0.29$), even when those patients who received all the elements of the care bundle were compared with those receiving some of the bundle elements (33 versus 61%, $P = 0.22$). Only Tagami *et al.* [57▪] reported a significant survival advantage in patients treated after the implementation of postresuscitation care; in a population of 1482 patients (770 before implementation and 712 after implementation), of which 346 achieved ROSC (158 before and 188 after), the combination of therapeutic hypothermia, early PCI if coronary thrombosis was the most likely cause of cardiac arrest, and hemodynamic management using transpulmonary thermodilution yielded an OR of 7.8 (95% CI 1.6–39.0, $P = 0.01$) for favorable neurological outcome when compared with standard therapy. Nevertheless, no specific hemodynamic targets were provided, so that it remains unclear the real impact of EGDHO on patients' outcome in this study. Moreover, only 2.3% of patients survived in the control group (before implementation), which is a very poor survival rate when compared with other series, thus limiting the generability of such results in countries with a much higher ROSC and survival rate, using different therapeutic protocols.

To summarize, there is no stunning evidence that early hemodynamic optimization (EHO) might really affect prognosis of cardiac arrest patients (Table 2). Unfortunately, studies on this topic included only limited cohorts of patients; also, the use of therapeutic hypothermia hampers the identification of some benefits in survival due to EGDHO itself. Finally, the adoption of supranormal values of $S_{cv}O_2$ (>75%) [55,56] could expose some patients to too high oxygen delivery and use of inotropes/vasopressors, with the risk of increasing side effects of therapy without substantial improvement in organ perfusion [58]. As some recent retrospective evidence pointed out a small but significant correlation between hemodynamic variables (mainly cardiac index and mean perfusion pressure) and 28-day neurological outcome [59▪], EGDHO should be focused on optimizing brain perfusion; the use of additional tools aimed at monitoring of cerebral oxygenation, including jugular saturation or near infrared spectroscopy,

Table 2. Summary of studies dealing with strategies to improve early goal-directed hemodynamic optimization

Author	Type of study	Intervention	Number of patients (treatment/control)	Survival treatment versus control	Neurological outcome (CPC 1-2) treatment versus control
Gaieski [55]	OPS	EGDHO + TH	38 (20 + 18 historical control)	50 versus 22%	44 versus 22%
Walters [56]	OPS	EGDHO + TH	55 (29+26 historical control)	45 versus 31%	31 versus 12%
Tagami [57▪]	OPS	EGDHO + TH + PCI	1482 (712 + 770 before campaign)	4 versus 2%*	3 versus 0.5%**

CPC, Cerebral Performance Category; EGDHO, early goal-directed hemodynamic optimization; OPS, observational prospective study; PCI, percutaneous coronary intervention; TH, therapeutic hypothermia.
*$P = 0.04$.
**$P < 0.01$.

would help select patients who have actually signs of PCAS, in whom hemodynamic management should prevent secondary brain injury and optimize brain oxygenation.

NEW STRATEGIES: WHAT IS NEW IN THE PIPELINE?

In the recent past years, some animal studies focused on alternative strategies that could further increase brain protection immediately after ROSC. Amongst all, interesting findings are available for inhaled noble gases, nitric oxide, and erythropoietin.

Noble gases, particularly xenon and argon, have been known to exert some neuroprotective effect *in vitro*, so they have been tested in animal models of cardiac arrest [60,61]. Combination of oxygen and xenon as inhaled mixture has been proved to reduce the extent of neurological damage after ischemia due to cardiac arrest [62]. Fries *et al.* [63▪], in a porcine model of cardiac arrest, applied 1 h of ventilation with oxygen and xenon (FiXe = 70%, $FiO_2 = 30\%$) to animals treated with therapeutic hypothermia and showed a significant improvement in functional neurological recovery and myocardial dysfunction. Moreover, another recent article evaluated the feasibility of xenon in a human setting reporting both no adverse effects and an amelioration of cardiovascular function after cardiac arrest [64▪]. Unfortunately, we still do not have any human data describing the potential neurological benefits of such treatment. Argon has also been tested in the last years, as a cheaper alternative to xenon. Brucken *et al.* [65] treated Sprague–Dawley rats 1 h after successful CPR with either ventilation combining 30% oxygen and 70% argon ($n = 7$) or only 30% oxygen ($n = 7$). Treated animals showed a significant reduction in histopathological damage of the neocortex and hippocampus, and a marked improvement in functional neurological recovery [65]. Similarly, Ristagno *et al.* [66▪] administered argon in a porcine model of cardiac arrest due to acute myocardial infarction after occlusion of the left anterior descending coronary artery. The intervention group ($n = 6$) received 4 h ventilation with oxygen 30% and argon 70% and had a better neurological outcome at 72 h (neurological alertness score: 100 versus 79, $P < 0.01$; neurological deficit: 0 versus 29, $P < 0.05$) than controls. Also, serum neuronal-specific enolase (NSE), a biomarker of postanoxic brain injury, showed a smaller increase (12 versus 234%) from baseline levels and histological brain injury was less extended in the argon than in the control group.

Nitric oxide inhibits ROS-producing enzymes and directly scavenges ROS production, thus reducing the extent of postanoxic injury; the effects of nitric oxide are mediated both via the soluble guanylate cyclase (sGC)–cyclic guanylate monophosphate (cGMP) path way, and via other complex intracellular pathways [67]. Other potential beneficial effects are the direct vasodilation of coronary arteries of nitric oxide, which could improve cardiac function in this setting. Experimental models have suggested a protective role of nitric oxide both on cardiac and neurological functions after cardiac arrest [68,69]. In order to avoid the systemic hypotension induced by nitric oxide, inhaled nitric oxide (iNO) at 40 ppm for 23 h after ROSC has been tested, yielding also very good results in terms of cardiac and neurological recovery in a murine model of cardiac arrest [70]. Interestingly, the use of therapeutic hypothermia may activate nitric oxide pathways, especially in the heart, so that a combination of these two therapeutic strategies should be considered to treat postanoxic injury [71]. Unfortunately, no study has tested the effects of nitric oxide-donor agents in patients with postanoxic injury [72]; only preliminary data showed that low-dose nitrite infusion did not result in hypotension or cause methemoglobinemia in cardiac arrest survivors [73▪] but did not report any improvement in outcome.

Erythropoietin (EPO), the principal hematopoietic hormone regulating erythropoiesis, exhibits various cellular effects in other tissues; particularly, due to its antiapoptotic, anti-inflammatory, and antioxidant properties, EPO plays a role in neuroprotection and cardioprotection [74]. In animal models, high-dose EPO administration during CPR reduced postresuscitation myocardial dysfunction and promoted hemodynamic stability in a swine model of ventricular fibrillation [75]. However, postischemic EPO administration was not neuroprotective on hippocampal neurons in a rat model of cardiac arrest, but significantly improved memory performance in treated animals [76]. Finally, survival to 72 h was significantly improved in the EPO group ($n = 15/17$) compared with the control group ($n = 7/17$) [77]. One human study has compared the effects of 90.000 UI of EPO given during CPR to a historical matched control group [78]. The EPO group had higher rates of ROSC (92 versus 53%, $P = 0.006$), 24-h survival (83 versus 47%, $P = 0.008$), and hospital survival (54 versus 20%, $P = 0.011$) when compared with the control group. In another study [79], EPO therapy was associated with a trend toward higher 28-day survival (55 versus 47%) and full neurological recovery (55 versus 38%) when compared with a historical cohort. Thus, future RCTs will provide new insights into the role of EPO on the outcome of cardiac arrest survivors.

CONCLUSION

The crucial importance of therapeutic hypothermia in improving prognosis after cardiac arrest brought many authors to test the hypothesis that the earlier the therapeutic hypothermia was started, the better it was. Yet all the evidence so far has severely questioned this assumption. The impact of a quite large amount of cold fluids used to induce therapeutic hypothermia may explain, at least in part, these controversial results, as also shown in a large recent RCT. IATH achieved without fluid infusion seems more promising, and its effectiveness is being tested in a large ongoing RCT. Even if EGDHO has been shown to be crucial in other emergency situation, no data clearly pointed out safety thresholds in the first phase after ROSC. Finally, some new therapies, including inhaled gases, nitric oxide, and EPO, are still under investigation and some of them are likely to be tested in a clinical scenario in a few years.

Acknowledgements

The figures presented in this review are original.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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