

REVIEW

Current Pharmacological Advances in the Treatment of Cardiac Arrest

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ABBREVIATIONS

AHA = American Heart Association
ALS = advanced life support
CPR = cardiopulmonary resuscitation
EMS = emergency medical services
ERC = European Resuscitation Council
IV = intravenous
PEA = pulseless electrical activity
ROSC = return of spontaneous circulation
VF = ventricular fibrillation
VSE = vasopressin-steroids epinephrine
VT = ventricular tachycardia

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ABSTRACT

Cardiac arrest requires immediate treatment, in order to prevent patient death. Cardiac arrest outcomes still remain very poor, especially when the patient requires vasopressor treatment. Vasopressors have been advocated, in order to increase the coronary and cerebral perfusion pressure during cardiopulmonary resuscitation (CPR). Recent data suggest an epinephrine-related benefit with respect to short- and long-term outcomes, only when epinephrine is administered within the first 10 min of collapse. Also, increasing the epinephrine dosing interval from 3-5 to 6-10 min during CPR may be associated with improved long-term outcomes. In the in-hospital setting, the combination of vasopressin, epinephrine, and corticosteroid supplementation during and after CPR (in the presence of post-resuscitation shock) may be superior to epinephrine alone during CPR. The use of new formulations of amiodarone, potentially devoid of serious hypotensive effects, may contribute to increased rates of sustained return of spontaneous circulation in patients with ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest. Encouraging preliminary results have been reported on the use of beta blockers in patients with shockable cardiac arrest. Other potentially promising pharmacological interventions include the use of cariporide, nitrates (and particularly inhaled nitric oxide), noble gases, levosimendan, and erythropoietin. The purpose of the current paper is to review the clinical and laboratory evidence that support new and potentially useful pharmacological interventions during CPR.

INTRODUCTION

Despite important advances in prevention, cardiac arrest remains a substantial public health problem and a leading cause of death in many parts of the world.¹ Cardiac arrest continues to be an all-too-common cause of premature death, and small incremental improvements in survival can translate into thousands of lives saved every year. In each resuscitation scenario, four concepts should always apply:

1. Activate the resuscitation team.
2. Perform cardiopulmonary resuscitation (CPR).
3. Evaluate heart rhythm and perform early defibrillation as indicated.
4. Deliver advanced life support (ALS), e.g., endotracheal intubation, intravenous

(IV) access and drugs, and specific treatment of reversible cardiac arrest causes.

There is an ongoing discussion concerning interventions to improve survival rates. Some interventions have strong evidence such as prompt initiation of high quality chest compressions,² early defibrillation,^{3,4} minimizing interruption in chest compressions,² and post resuscitation care initiatives.⁵⁻⁷ Conversely, interventions such as intravenous vasopressor agents have a controversial role in resuscitation.^{8,9} In this paper, we summarize current experimental and clinical data on drugs during CPR.

VASOPRESSORS

To date, no controlled trials have shown that administration of any vasopressor agent at any stage during the management of any cardiac arrest rhythm, i.e. ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT), pulseless electrical activity (PEA), and asystole, increases the rate of neurologically favorable survival to hospital discharge.

EPINEPHRINE

Epinephrine is a non-selective alpha and beta adrenergic agonist, and its value in resuscitation is attributed largely to the alpha-1 receptor mediated vasoconstrictive properties.⁸ It has been used in CPR since 1896⁹ and it is integrated into advanced life support guidelines for adult cardiac arrest.^{10,11} Apart from increased rates of return of spontaneous circulation (ROSC),¹⁰⁻¹² there are limited data supporting epinephrine effectiveness with respect to long-term survival.¹²

Epinephrine augments coronary blood flow generated by chest compressions during CPR. After a few minutes of cardiac arrest, arterial tone collapses and epinephrine or another vasoconstrictor is essential for the restoration of spontaneous cardiac activity.¹³⁻¹⁵ Epinephrine increases aortic pressure during chest compressions via alpha-adrenergic constriction of arterioles, which increases pressure in the proximal aorta.¹⁶ Increased aortic pressure may shunt more blood into the coronary arteries and increase the probability of ROSC.

Beta-adrenergic effects of epinephrine are generally undesirable for cardiac arrest patients. Beta-adrenergic stimulation causes tachycardia, tachyarrhythmias and increased myocardial oxygen consumption, exacerbating a possible existing myocardial insult.¹⁷ It also renders ventricular pacing foci irritable and increases the probability of ventricular arrhythmias post-resuscitation.¹⁸ Epinephrine may also promote thrombogenesis and platelet activation.¹⁹ Acute coronary syndromes are the most common cause of sudden cardiac arrest in a series of resuscitated out-of-hospital cardiac arrest patients.²⁰ Increased platelet activity might worsen acute coronary ischemia.

Vasoconstriction induced by epinephrine prolongs ischemia in some tissue beds during and after CPR.²¹ Regarding

the brain, the alpha-1 agonist activity of epinephrine has been associated with reduced perfusion of the cerebral microcirculation,^{22,23} which may explain previously reported, unfavorable results on neurological outcomes.^{24,25}

Epinephrine has been compared with several vasoactive medications that might increase coronary perfusion pressure in clinical trials.²⁶⁻²⁸ In particular, studies have found no consistent superiority of epinephrine over other alpha-adrenergic agonists or more recently vasopressin.

Nonrandomized studies^{24,29-33} suggest that neurological outcomes may be worse with epinephrine. Also, two randomized clinical trials failed to show a beneficial effect of epinephrine on long-term survival. In the first study, which took place in Oslo, Norway, adult, out-of-hospital cardiac arrest victims were randomly assigned to receive intravenous (IV) drugs versus no IV drugs.^{17,34} Among the 851 patients who were included in the primary analysis, 418 had IV access and 433 had no IV access. In 45 patients (10%) assigned to no IV drugs, an IV drug administration did occur later-on during resuscitation. In 74 patients (17%) assigned to IV drugs, no line could be established prior to the end of resuscitation.

Patients with vs those without an IV line had higher rates of ROSC (40% vs 25%) and admission to the intensive care unit (ICU) (30% vs 20%). However, the proportions of patients discharged from the hospital (10.5% vs 9.2%) or alive at 1 year (10% vs 8%) were similar. The most commonly administered IV drug was epinephrine (79% of the patients with intravenous access).

In a *post-hoc* analysis published later-on, the authors compared outcomes between patients who actually received epinephrine and those who did not receive epinephrine.¹⁷ Patients who received epinephrine (n=367) versus those who did not receive epinephrine (n=481) were more likely to achieve hospital admission (odds ratio - OR: 2.5, 95% confidence interval - CI: 1.9-3.4) but less likely to survive to hospital discharge (OR: 0.5, 95% CI: 0.3-0.9).

In the second study, which was conducted in Australia, adult, out-of-hospital cardiac arrest patients were randomized to receive 1-mg boluses of epinephrine or placebo.³⁵ Blinding was achieved by supplying paramedics with identical vials containing either 1 mg/mL of epinephrine or saline placebo. From 602 randomized patients, 534 (epinephrine group, n=272) had available documentation and were included in the primary analysis.

Epinephrine vs placebo group patients were more likely to achieve ROSC (OR=3.4; 95% CI 2.0-5.6) but not survival to hospital discharge (OR=2.2; 95% CI 0.7-6.3). This study did not achieve its intended enrolment target because of problems with funding and loss of support from the participating paramedics.

Notably, a recent, retrospective analysis of prospectively collected, population-based data (n=49165 adults with witnessed, out-of-hospital cardiac arrest of cardiac origin) showed

that epinephrine administration within 10 minutes of collapse was associated with improved survival to hospital discharge (OR 1.73; 95% CI: 1.46-2.04) and good neurological outcome (OR 1.39, 95% CI 1.08-1.78).³⁶ In most studies, good neurological outcome is defined as a cerebral performance category score of 1 or 2³⁷ at hospital discharge. Epinephrine efficacy is also supported by another, large, propensity analysis that showed a slightly improved, neurologically favorable survival with epinephrine use vs no use (0.7% vs 0.4%; OR: 1.57, 95% CI: 1.04-2.37) in 9058 pairs of patients with non-shockable out-of-hospital cardiac arrest.³⁸

Lastly, another recent review of 20909 in-hospital cardiac arrest events showed that increasing the epinephrine dosing interval from the guideline-recommended of 3-5 minutes to 6-10 minutes was associated with improved survival to hospital discharge (adjusted ORs 1.30 to 2.17; 95% CIs: 1.02-1.62 to 1.65-2.92).³⁹ Consequently, both the optimal timing of the first dose of epinephrine and its optimal dosing interval warrant further determination in future, prospective, randomized clinical trials.

VASOPRESSIN WITH/WITHOUT STEROIDS

Vasopressin causes contraction of vascular smooth muscle through stimulation of the V1a receptors and increases smooth muscle responsiveness to catecholamines.⁴⁰ Endogenous vasopressin and cortisol levels are higher in patients achieving ROSC.⁴¹ Furthermore, experimental data suggest that vasopressin improves vital organ perfusion during CPR, post-ROSC survival, and neurological recovery.⁴²⁻⁴⁷

In the 2010 American Heart Association guidelines for CPR, the authors state "Because the effects of vasopressin have not been shown to differ from those of epinephrine in cardiac arrest, 1 dose of vasopressin 40 units intravenous/intraosseous may replace either the first or second dose of epinephrine in the treatment of cardiac arrest" (Class IIb, Level of Evidence A).¹¹ On the other hand, authors of the European Resuscitation Council (ERC) guidelines, do not support the use of any other vasopressor instead of or in addition to epinephrine.¹⁰ They emphasize on the scarcity of data to support or refute the use of any vasopressor during cardiopulmonary resuscitation efforts. The use of epinephrine is still recommended by the ERC guidelines, based solely on animal data and increased short-term survival in humans.^{31,34}

In a meta-analysis conducted by our group,⁴⁸ we included data from 6 high-methodological quality randomized controlled trials^{27,28,49-52} that enrolled a total of 4475 patients. These trials assigned adults with cardiac arrest to treatment with either a vasopressin-containing regimen (vasopressin-group), or epinephrine alone (control-group). Subgroup analyses were conducted according to initial cardiac rhythm and time from collapse to drug administration less than 20 minutes.⁴⁸ Vasopressin use was not associated with any overall benefit or harm. However, in asystole, vasopressin vs control

was associated with higher long-term survival (OR: 1.80, 95% CI: 1.04-3.12). Furthermore, in asystolic patients with a time from collapse to drug administration of less than 20 minutes, vasopressin vs control increased the rates of sustained ROSC (data available from 2 trials; OR = 1.70, 95% CI = 1.17-2.47) and long-term survival (data available from 3 trials; OR = 2.84, 95% CI = 1.19-6.79).

A more recent, multicenter clinical trial recruited 727 participants and evaluated vasopressin (40 IU) vs epinephrine (1 mg) given to out-of-hospital, non-traumatic, adult cardiac arrest patients brought to the Emergency Department,⁵³ additional epinephrine was administered as required according to resuscitation guidelines.⁵³ Eleven participants from the vasopressin group (2.9%) and 8 participants from the epinephrine group (2.3%) survived to hospital discharge with (OR: 1.72, 95% CI: 0.65-4.51). After adjustment for race, medical history, bystander CPR, and pre-enrolment epinephrine, vasopressin-treated patients were more likely to achieve hospital admission than epinephrine-treated patients (OR: 1.43, 95% CI: 1.02-2.04). Sub-group analysis suggested improved outcomes with vasopressin treatment in participants with prolonged arrest times. The authors emphasized the need for further studies on the effect of vasopressin combined with therapeutic hypothermia in patients with prolonged cardiac arrest.

In a previous single-center, randomized, controlled study conducted by our group,⁵² combined vasopressin-epinephrine during CPR and corticosteroid supplementation during and after CPR vs epinephrine alone during CPR and no steroids resulted in improved overall survival to hospital discharge. Patients in the vasopressin-steroids epinephrine (VSE) group had more frequent ROSC, and attenuated post-resuscitation systemic inflammatory response^{52,54} and organ dysfunction.⁵² This preliminary study could not reliably assess VSE efficacy with respect to neurologically favorable survival to hospital discharge. We addressed this question in a subsequent, 3-center study of vasopressor-requiring, in-hospital cardiac arrest;⁵⁵ the study protocol was identical to that of our preliminary study.⁵² This randomized, controlled trial included 268 consecutive patients with cardiac arrest requiring epinephrine according to resuscitation guidelines (from 364 patients assessed for eligibility). Patients received either vasopressin (20 IU/CPR cycle) plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 min) (VSE group, n = 130) or saline placebo plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 min) (control group, n = 138) for the first 5 CPR cycles after randomization, followed by additional epinephrine if needed. During the first CPR cycle after randomization, patients in the VSE group received 40 mg of methylprednisolone and patients in the control group received saline placebo. Shock after resuscitation was treated with stress-dose hydrocortisone (VSE group) or saline placebo (control group). Patients in the VSE group vs patients in the control group had higher probability of ROSC for 20 minutes or longer (83.9% vs. 65.9%;

OR: 2.98, 95% CI: 1.39-6.40) and survival to hospital discharge with a cerebral performance category score of 1 or 2 (13.9% vs. 5.1%; OR: 3.28; 95% CI 1.17-9.20).

Both VSE studies exhibit limitations: results refer only to in-hospital cardiac arrest, there was no assessment of CPR quality, the VSE protocol did not allow a precise determination of the relative contribution of vasopressin and steroids to the positive VSE group outcomes, there were some baseline imbalances with respect to cardiac arrest etiology and presenting rhythm, potentially favoring the VSE group,^{52,55-58} and there was no pre-specified determination of 1-year outcomes. Thus, additional clinical evaluation is warranted before the incorporation of the VSE protocol to the resuscitation guidelines.⁵⁹

Additional CPR drug regimens supported by animal data and potentially warranting further clinical evaluation may include combined epinephrine, vasopressin, and nitroglycerin,⁶⁰ epinephrine and atenolol,⁶¹ epinephrine and nitroglycerin,⁶² and epinephrine and levosimendan.⁶³

ANTIARRHYTHMICS

Antiarrhythmics are a heterogeneous group of drugs that affect cardiac automaticity and conduction, and are used for ventricular and atrial arrhythmias.

AMIODARONE

Amiodarone is a potent antiarrhythmic agent with a complex electrophysiological and pharmacological profile.⁶⁴ It is primarily a Vaughan Williams Class III agent; it acts by inhibiting the inward potassium current. It also blocks sodium and calcium channels and has antiadrenergic properties (noncompetitive blockade of alpha and beta receptors). It prolongs the action potential and the QT interval, and increases the refractoriness of the cardiomyocytes. Amiodarone is effective in suppressing both supraventricular and ventricular tachyarrhythmias.

The treatment of choice for ventricular fibrillation (VF) is defibrillation. However, amiodarone can be useful in shock refractory VF. In the Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST) trial, amiodarone was shown to improve survival to hospital admission (when compared to placebo) in patients with shock-refractory VF.⁶⁵ On the basis of these results, the current VF guidelines (both AHA and ERC) suggest amiodarone in shockable rhythms not responsive to three countershocks and vasopressor therapy (Class IIb, Level of Evidence B).^{10,11} An initial dose of 300 mg (IV or intraosseously) can be followed by a second dose of 150 mg. Amiodarone is more effective than lidocaine in VF or pulseless ventricular tachycardia (VT).^{11,66}

Amiodarone has a relatively slow onset of action with a maximum effect at 15 minutes after IV injection. A possible reason of drugs' failure to improve long-term survival is that

they are given too late during ALS.⁶⁷ Also amiodarone's efficacy as rescue medication may be hampered by its hypotensive and bradycardic activity, especially in patients with heart failure.⁶⁸

Indeed, in the ARREST trial, amiodarone treated patients experienced more bradycardia and hypotension.⁶⁵ Hypotension is the dose-limiting adverse event of IV amiodarone and may be partly due to the formulation's cosolvents (i.e. polysorbate 80 and benzyl alcohol). To minimize hypotension, the initial loading dose of amiodarone is diluted to 1.5 mg/ml and infused over 10 minutes.

As rapid drug administration may be important, efforts have been focused on the development of alternative amiodarone formulations. In 2008, an amiodarone formulation with sulfobutylether-7-beta-cyclodextrin (Nexterone[®]) was approved by the FDA, with the same label indications as the previously approved formulation of amiodarone. The formulation's diluent is hemodynamically and electrophysiologically inert.⁶⁹ Captisol-enabled amiodarone as rapid IV bolus (150 mg) and as continuous infusion is bioequivalent to the previous approved formulation of amiodarone, with identical electrophysiologic effects,⁷⁰ but no hypotensive effects.^{71,72}

LIDOCAINE

The Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) trial involved 347 patients randomized to either amiodarone (initial bolus dose of 5mg/Kg followed, if needed, by a second bolus dose of 2.5 mg/Kg) or lidocaine (initial bolus dose of 1.5 mg/Kg, repeated once, if needed). More patients treated with amiodarone survived to hospital admission, compared with patients treated with lidocaine (23% versus 12%, $P < 0.005$).⁶⁷

A recent systematic review of the literature regarding amiodarone and lidocaine and their effectiveness in cardiac arrest patients, reached the conclusion that "Amiodarone may be considered in patients with refractory VF/VT, defined as VF/VT/VF not terminated by defibrillation, or recurring VF/VT. There is inadequate evidence to support or refute the use of lidocaine and other antiarrhythmic agents in the same settings".⁷³

According to current guidelines,^{10,11} if amiodarone is not available, the sodium channel blocker lidocaine may be given (initial IV bolus: 1-1.5 mg/kg, followed by additional IV boluses of 0.5-0.75 mg/kg every 5-10 minutes and up to a total dose of 3 mg/kg). A large effectiveness trial comparing amiodarone, lidocaine, and placebo in non-traumatic out-of-hospital cardiac arrest due to shock-refractory VF/VT is currently underway.

NIFEKALANT

Nifekalant is a selective potassium channel blocker. In a porcine model of induced VF, nifekalant and amiodarone were equally effective in improving short-term survival and postresuscitation cardiac function.⁷⁴ Nifekalant was reported to be associated with improved short-term survival when it was used

in the management of shock-refractory VF/VT cardiac arrest.^{75,76}

BETA BLOCKERS

Two small, clinical, prospective human studies tested the effects of beta blockade against regular therapy in patients presenting with electrical storm. Electrical storm, defined as recurrent multiple VF episodes, often occurs in patients with recent myocardial infarction, and bears a poor prognosis. In the intervention group of the first study,⁷⁷ sympathetic blockade (left stellate ganglionic blockade, esmolol, or propranolol) resulted in a decline in the mean number of VF episodes from over 20 to 2.6 ± 1.7 per day ($P < 0.01$). In contrast, 91% of patients in the control group continued to have VF episodes. At the end of the first year of follow-up, 18/27 patients in the beta blockade group were still alive, compared with 1/22 in the control group. In the other human trial,⁷⁸ 42 consecutive patients with electrical storm refractory to regular ALS therapy received intravenous landiolol in increasing doses (starting at $2.5 \mu\text{g}/\text{kg}/\text{min}$; maximum dose was $80 \mu\text{g}/\text{kg}/\text{min}$), subsequently titrated to the minimum infusion rate required for arrhythmia control. The study protocol was ineffective in 9 patients (21%), who died of arrhythmia. From the 33 responders, 21 received carvedilol and 12 were started on bisoprolol, with oral beta-blocker administration immediately after stabilization. Eight of these 33 patients (19%) died afterwards from multiple organ failure or infection, and 25 (60%) survived to hospital discharge.

A recently published review on the use of beta-blockers in cardiac arrest with shockable rhythms concluded that available human studies may point toward a beneficial effect of beta-blockade in patients, which is in accordance with the results from the majority of relevant clinical case reports and animal experimental studies.⁷⁹ However, high quality human trials are warranted, in order to reliably evaluate the potential usefulness of the beta-blockers in cardiac arrest. Indeed, beta-blockers may counteract the potentially deleterious beta-adrenergic effects of epinephrine, which may contribute to the post-resuscitation myocardial dysfunction and the recurrence of life-threatening arrhythmias.

MAGNESIUM SULPHATE

According to current AHA and ERC guidelines, IV magnesium sulfate can be given exclusively for the treatment of irregular/polymorphic VT associated with prolonged QT interval.^{10,11,80,81} A recent meta-analysis concluded that IV magnesium sulfate vs placebo does not affect short- or long-term outcomes of cardiac arrest.⁸²

OTHER DRUGS

CARIPORIDE

Ventricular arrhythmias commonly occur after successful

resuscitation from cardiac arrest with a reported incidence of VF as high as 79%.⁸³ Some studies have reported an inverse relationship between the number of VF episodes and survival.⁸³ Along with reperfusion arrhythmias, the myocardium during the post resuscitation period also suffers varying degrees of global dysfunction that can compromise hemodynamic function.^{84,85} Resuscitation from cardiac arrest is commonly associated with varying severity of reversible left ventricular systolic and diastolic dysfunction.^{86,87} These electrical and mechanical abnormalities occur early in the post-resuscitation phase, and contribute to re-arrest and early post-ROSC mortality.⁸⁶

The Na^+ -induced, cytosolic Ca^{2+} overload plays a prominent role in the ischemia/reperfusion injury of the cardiomyocytes. Electrophysiologically, there are repolarization abnormalities, including shortening of action potential duration; post-resuscitation ventricular arrhythmias are partly due to cytosolic Ca^{2+} accumulation.⁸⁸⁻⁹¹ This reflects a reverse operation of the sarcolemmal Na^+ - Ca^{2+} exchanger.^{92,93} More specifically, during ischemia, intracellular acidosis develops rapidly and the sarcolemmal sodium-hydrogen exchanger isoform-1 (NHE-1) is activated, with concomitant inactivation of the Na^+ - K^+ ATPase.^{94,95} Na^+ accumulates intracellularly, activating the Na^+ - Ca^{2+} exchanger, and increasing the cytosolic Ca^{2+} . This can lead to detrimental cardiomyocyte injury, such as contracture and necrosis. During myocardial reperfusion, these events are magnified because the return of blood flow lowers the extracellular H^+ concentration, thus stimulating the NHE-1 to extrude more intracellular H^+ ion. This leads to further intracellular Na^+ entry, and ultimately intracellular Ca^{2+} overload (through the Na^+ - Ca^{2+} exchanger) and cardiomyocyte injury.⁹⁶

NHE-1 inhibition could reduce sarcolemmal Na^+ entry and spare ATP use by the Na^+ - K^+ pump, thus retarding intracellular ATP depletion and the consequent ischemic contracture.⁹⁷ Reduced cytosolic Na^+ overload might attenuate/prevent 1) the associated mitochondrial injury;⁹⁸ and 2) the reverse-mode operation of the Na^+ - Ca^{2+} exchanger; this causes cytosolic Ca^{2+} overload, as well as an outward (repolarizing) current that shortens action potential duration and promotes electrical instability. Excellent reviews have been written on the mechanisms of NHE-1 activation and the potential benefits of its inhibition.^{99,100}

Cariporide is a potent and specific NHE-1 inhibitor. Several experimental studies showed beneficial effects of NHE-1 inhibitors given at the onset of resuscitation.^{94,95,101-112} During VF, NHE-1 inhibition attenuated/prevented the development of ischemic contracture, and post-resuscitation ventricular ectopic activity, episodes of recurrent VF, and myocardial dysfunction. NHE-1 inhibition facilitated successful resuscitation and improved survival.¹⁰⁵ Clinical studies on NHE-1 inhibition during cardiac resuscitation will shed more light into their effectiveness in humans.

NITRATES

The greatest proportion of in-hospital, post-resuscitation mortality is caused by global ischemic brain injury, whereas both myocardial dysfunction and systemic inflammation predispose to poor neurological outcome.¹¹³ Mechanisms of post-resuscitation brain injury include excitotoxicity, free radical formation, pathological activation of proteases, and cell death signalling.¹¹⁴ The injurious pathways include disruption of the blood–brain barrier, neuro-inflammation, and delayed neuro-degeneration.^{113,115}

Nitrite therapy limits cellular injury and apoptosis after ischemia and reperfusion (I/R).¹¹⁶ It has been proven to be cytoprotective in numerous animal models of focal I/R injury, including rodent heart, brain, liver and kidney, canine heart, and primate brain.¹¹⁶⁻¹²⁰ Systemic nitrite reduction by ceruloplasmin knockout or dietary nitrate/nitrite elimination increased infarction volume in the liver and heart after experimental ischemia.^{121,122} These studies indicate that physiological systemic nitrite levels modulate host resilience to ischemia. The established safety of human and animal nitrite dosing¹²³ and its potent effects in limiting major organ injury suggest that nitrite represents an ideal candidate for the treatment of cardiac arrest.

Nitric oxide (NO) is produced from NO synthases (NOS, i.e. NOS1, NOS2, and NOS3). NO exerts a number of effects that would be expected to be beneficial during I/R injury.¹²⁴ NO is a potent vasodilator which inhibits platelet and leukocyte activation and adhesion, inhibits reactive oxygen species (ROS)-producing enzymes, and directly scavenges ROS.¹²⁵ Studies using NOS3 knockout mice showed that NOS3 deficiency aggravates I/R injury in the brain and heart,^{126,127} whereas cardiomyocyte-specific overexpression of NOS3 attenuated postresuscitation myocardial and neurological dysfunction in NOS3-deficient mice.¹²⁸

Several recent studies are also consistent with a nitrite treatment/NO associated benefit in experimental cardiac arrest.^{60,62,129-134} Likely mechanisms of brain protection may involve the primary intra-cellular target of NO, i.e. soluble guanylate cyclase,¹³² or increased levels of neuronal nitrite and S-nitrosothiols.¹³³ The neuroprotective effects of hypothermia seem to be at least partly mediated through enhanced NOS3 signalling.¹³⁴ Also, inhaled NO (40 ppm) improves neurological outcomes during concurrent use of hypothermia.¹³⁴

In contrast to NO, NO-donor compounds may induce systemic vasodilation and hypotension, frequently precluding their use in the setting of cardiac arrest-associated hemodynamic instability. On the other hand, inhaled NO is a selective pulmonary vasodilator that does not produce systemic hypotension when inhaled at concentrations of up to 80 ppm in multiple species, including man.¹³⁵ The absence of systemic vasodilation during NO inhalation is due to the rapid scavenging of NO by hemoglobin in the blood.

Some NO, once inhaled, may escape scavenging by hemo-

globin and be converted to relatively stable NO metabolites (e.g., nitrite and S-nitrosothiols) that can regenerate NO in the periphery.¹³⁶ NO inhalation has been associated with marked increases in the arterial blood concentration of NO metabolites.¹³⁷ Also, regenerated NO may exert regional vasodilating effects. Indeed, a recent study by Terpolilli et al,¹³⁸ showed that NO inhalation prevented ischemic brain injury in mice and sheep by selective dilatation of collateral arterioles. The aforementioned, promising, experimental results provide a robust background for a possible, future evaluation of nitrates/NO in the clinical setting

NOBLE GASES

A major post-ROSC threat is global cerebral hypoxia-ischemia,^{139,140} which causes necrosis or apoptosis of neuronal tissue.¹⁴¹⁻¹⁴³ Cognitive dysfunction, a permanent or transient inability to perform daily activities^{144,145} is an expected result, especially due to hippocampal injury.¹⁴⁶⁻¹⁴⁸ It is imperative that survival rates after cardiac arrest and attempts to improve these rates be seen under the spectrum of long term neurological recovery. Many experimental and clinical studies focus on novel strategies to improve these rates.

Medical gases (hydrogen, helium, argon, xenon) have a wide scope of applications in medicine, such as anesthesiology, hyperbaric oxygen therapy, neuroprotection and hypothermia.¹⁴⁹

1. Xenon

Xenon is a noble gas with anesthetic properties. It is a potent and specific competitive antagonist of the N-Methyl-D-Aspartate (NMDA) receptor.^{150,151} The NMDA receptor is a ligand-gated ion channel, which allows the selective passage of both Na⁺ and Ca²⁺ ions into cells. These receptors are vital in neural plasticity, learning, memory, pain and, most crucially, glutamate-mediated neurotoxicity.¹⁵² Xenon also inhibits two other subtypes of glutamate receptor channels, namely the AMPA(α -Amino-3-hydroxy-5-Methyl-4-isoxazole-Propionic Acid) and KA (Kainate) receptors,¹⁵³ as well as the recently identified two-pore potassium channels, TREK.^{154,155} It also activates ATP-sensitive K⁺ channels.¹⁵⁶

In vivo studies using subanesthetic (i.e. 50%) concentrations of Xenon showed promising results against cardiac arrest-induced cerebral ischemia,¹⁴⁸ and neurobehavioral dysfunction due to a brain insult.¹⁵⁶ Xenon attenuates the ischemia-induced, neurotransmitter release,¹⁵⁴ and antagonizes NMDA receptors.^{148,157-159} Xenon's blockade of NMDA receptors is a key factor,¹⁵⁰ since NMDA receptors are primarily involved in the initiation and progression of apoptosis of neural tissue.^{160,161} Xenon treatment reduces perivascular inflammation in the putamen and caudate nucleus of pigs resuscitated from cardiac arrest.¹⁴⁸ Xenon has a higher efficacy in the cortex rather than the subcortex due to differences in the vascularity and density of the NMDA receptors.¹⁶² Xenon also contributes to cardio-

vascular stability,¹⁶³ and myocardial protection.¹⁶⁴

Xenon has also been investigated in combination with therapeutic hypothermia. Studies have shown that Xenon augments neuroprotection when combined with hypothermia in animal hypoxia-ischemia models.¹⁶⁵⁻¹⁶⁷ Hobbs et al have demonstrated that a combination therapy of hypothermia (32°C) with inhalation of 50% Xenon for 3 hours increases neuroprotection from 37% (hypothermia only) to 76% (hypothermia combined with xenon inhalation).¹⁶⁸ Hypothermia decreases the release of glutamate that binds to NMDA receptors. It also reduces the release of glycine which assists glutamate to act on the NMDA receptor. Since Xenon is a NMDA receptor antagonist, hypothermia's role of decreasing neurotransmitter and Xenon's role of receptor blockage converge on an antiapoptotic pathway.¹⁶⁸

Arola et al assigned patients resuscitated from out-of-hospital VF/VT cardiac arrest to either therapeutic hypothermia alone or in combination with xenon (target concentration of at least 40%) for 24 hours.¹⁶⁹ The frequency of serious adverse events, including in-hospital mortality, status epilepticus and acute kidney injury, was similar in both groups and there were no unexpected serious adverse reactions to xenon. In addition, xenon did not induce significant conduction, repolarization, or rhythm abnormalities. The median dose of norepinephrine, heart rate, and incremental changes in cardiac troponin-T were lower in xenon-treated patients. The authors concluded that xenon treatment in combination with hypothermia is feasible and has favorable cardiac features in survivors of VF/VT cardiac arrest.

2. Argon

Argon is another noble gas, but unlike xenon, it is quite abundant in earth's atmosphere. As with xenon, no side adverse effects on its applications on humans have been reported.¹⁷⁰ Argon's lack of anesthetic properties and low cost, make it a more attractive candidate than xenon, in the research of noble gases' organoprotective properties.¹⁷¹

Prior experimental studies suggested that Argon may exert protective effects on the brain, heart and kidney.¹⁷²⁻¹⁷⁶ Ristagno et al investigated the effects of post resuscitation treatment with argon on neurological recovery in a porcine model of cardiac arrest with an underlying acute myocardial infarction. They concluded that post-resuscitation treatment with argon allowed for a faster and complete neurological recovery, without detrimental effects on hemodynamics and respiratory gas exchange.¹⁷⁷

The already published, preliminary data on Xenon and Argon are encouraging for further evaluation of their efficacy in the clinical setting.

CORTICOSTEROIDS

Recent laboratory data and clinical results are consistent with a possible, low-dose corticosteroid-associated, benefit in

cardiac arrest, especially in patients with post-resuscitation shock.¹⁷⁸

Cardioprotective effects of glucocorticoids in the acute setting of myocardial I/R have been shown experimentally with regard to structural and functional myocardial damage.¹⁷⁹⁻¹⁸⁶ A more recent meta-analysis of human data from 11 controlled trials suggested a possible mortality benefit for corticosteroid treatment of myocardial infarction.¹⁸⁷

Glucocorticoids attenuate leukocyte/endothelium interactions,¹⁸⁸⁻¹⁹¹ as well as the generation and release of inflammatory cytokines and mediators.¹⁹²⁻¹⁹⁵ The post-cardiac arrest syndrome has similarities to septic shock, but the efficacy of corticosteroids remains controversial in patients with sepsis as well.^{54,196-198} The Surviving Sepsis Campaign guidelines 2012 for the management of severe sepsis and septic shock suggest stress-dose hydrocortisone therapy (daily dose: 200 mg) only for patients who are poorly responsive to fluid and vasopressor therapy,¹⁹⁹ a state of shock very usual in cardiac arrest patients in the post resuscitation phase.

The mechanisms underlying the post-cardiac arrest syndrome involve a whole body ischemia and reperfusion that triggers a systemic inflammatory response.^{187,188,196,197,200} Altogether, the high levels of circulating cytokines, the presence of endotoxin in plasma, and the dysregulated production of cytokines found in cardiac arrest patients resemble the immunological profile found in patients with sepsis.²⁰⁰⁻²⁰²

In our recent, in-hospital cardiac arrest studies,^{52,55} we administered 40 mg of methylprednisolone during CPR (in combination with vasopressin / epinephrine – see section on vasopressors), and stress dose hydrocortisone (300 mg/day for a maximum of 7 days followed by gradual taper) to patients fulfilling a clearly defined criterion for post-resuscitation shock. Patients with evidence of myocardial infarction received a 3-day course of stress dose hydrocortisone (followed by gradual taper), in order to prevent any potential retardation of infarct healing. Compared to control, the postresuscitation shock subgroups of the VSE groups had improved post-arrest hemodynamics and central venous oxygen saturation,^{52,55} post-arrest cytokine levels⁵² and organ/system function^{53,56} and survival to hospital discharge with favorable neurological recovery.^{52,55} Accordingly, pooled subgroup results show more VSE patients [23/103 (22.3%)] than control patients [6/88 (6.8%)] with good functional outcome [Hazard ratio for death during follow-up or severe cerebral disability/vegetative state: 0.64; 95% CI 0.46-0.88; P=0.006].^{52,55}

As already mentioned above, due to the VSE combination, we could not separately assess glucocorticoid efficacy.^{52,55,202} Therefore, a large, multicenter, randomized, placebo-controlled evaluation of stress-dose glucocorticoid supplementation in cardiac arrest is still needed.^{178,202} Such a study should provide definitive results on the efficacy, and appropriate dosage and timing of steroid administration. Lastly, although there is no published data suggestive of a

glucocorticoid-associated neuroprotection,^{52,55,178,201,202} recent laboratory results suggest that the biosynthetically related estrogens may actually mitigate the effects of global cerebral ischemia,^{203,204} and renal ischemia as well.²⁰⁵

LEVOSIMENDAN

Levosimendan, a new calcium sensitizer, exerts positive inotropic and lusitropic effects in failing human myocardium without increase in energy expenditure.²⁰⁶ The documentation regarding levosimendan is one of the largest ever on the safety and efficacy of a pharmacological agent in acute heart failure syndromes.²⁰⁶ Recently, levosimendan, was tested alone in an asphyxia model of cardiac arrest.²⁰⁷ Levosimendan increased cerebral blood flow, reduced neuronal injury, and improved neurological outcome, when compared to placebo. Findings seem to be independent of inflammatory effects because no effects of levosimendan on cerebral or systemic inflammation could be detected. Another study reports favorable effects of levosimendan on cardiac function.²⁰⁸ It seemed to have better inotropic and lusitropic effects when compared to epinephrine, during rewarming from deep hypothermic circulatory arrest with cardiopulmonary bypass. Another study compared epinephrine to the combination of levosimendan and epinephrine in an experimental model of ventricular fibrillation.⁶³ The combination therapy seemed to significantly improve the rates of ROSC ($P = 0.01$). The coronary perfusion pressure, saturation of peripheral oxygenation and brain regional oxygen saturation were significantly higher during cardiopulmonary resuscitation in the group that received the combination of levosimendan and epinephrine. Epinephrine combined with levosimendan and atenolol, administered during resuscitation, in a pig model of cardiac arrest, resulted in improved 48-hour survival and improved postresuscitation cardiac function.⁶¹

ERYTHROPOIETIN

Several studies have shown that erythropoietin, besides its critical role in hematopoiesis, also activates potent cell survival mechanisms during ischemia and reperfusion through genomic and non-genomic signaling mechanisms in a broad array of organs and tissues including the brain,²⁰⁹⁻²¹² heart²¹³⁻²²² and kidney.^{223,224}

In one rat model of asphyxial cardiac arrest, the administration of erythropoietin 15 minutes before the arrest was associated with improved 72-hour survival.²²⁵ Another animal study demonstrated improved postresuscitation myocardial function and 3-day survival. During the latter study, erythropoietin was administered 3 minutes after ROSC.²²⁶

A human study of erythropoietin administered during CPR showed improved short-term and long-term survival when compared with (nonrandomized) concurrent, and retrospective controls.²²⁷ In this study, an IV bolus of 90,000 IU erythropoietin was given to out-of-hospital patients within

2 minutes of EMS arrival on the scene. The erythropoietin group, when compared to placebo and matched historic controls, was associated with more effective chest compressions leading to higher ROSC rate, 24-hour survival and survival to hospital discharge. However, the validity of these results is obscured by serious methodological flaws of the study, as the study design was abandoned in the interim and drugs were given in a non-randomized and open fashion allowing for various sources of bias.

The neuroprotective action of erythropoietin was tested in out-of-hospital patients in a matched control study by Cariou et al.²²⁸ Erythropoietin-alpha (40,000 IU, repeated every 12 hours for the first 48 hours) was administered after sustained ROSC and compared to placebo, while all the patients were admitted to the ICU and treated with mild hypothermia. After 28 days there was a trend toward better neurological recovery in the erythropoietin-treated group, which never reached statistical significance; thus, there was no difference in terms of survival. Thrombocytosis occurred in 15% of patients in the Epo-group, and was associated with one case of arterial vascular thrombosis.²²⁸ A large, randomized, controlled, phase III trial investigating the possible neuroprotective role of erythropoietin-alpha in comatose survivors of cardiac arrest is currently underway.

Due to its anti-apoptotic, anti-inflammatory, and anti-oxidant properties, as well as its angiogenic action, erythropoietin may have a role in neuroprotection and cardioprotection. In this regard, erythropoietin represents a promising agent as part of the post-resuscitation treatment of cardiac arrest patients.²²⁹

CONCLUSIONS

Early recognition and activation, uninterrupted chest compressions of appropriate depth (at least 51 mm) and rate (100/min), while still allowing for full chest recoil, and early defibrillation (when the rhythm is shockable), are components of CPR proven to increase the probability of neurologically favorable survival. Effective chest compressions remain the mainstay of CPR. In between the 5-yearly guideline updates and despite the abundance of publications, it hasn't been feasible to definitively support or refute the use of ANY single drug during cardiopulmonary resuscitation. Use of vasopressors as described in international guidelines published by AHA or ERC, is based mainly on experimental and observational data. The efficacy of a regimen of vasopressin, epinephrine during CPR, and of steroids "during/after CPR" requires further confirmation in a multinational trial involving multiple healthcare systems. It is widely accepted that short-term benefits of CPR drug regimens may be converted into long-term outcomes by optimizing management in the postarrest period; thus, further research is warranted in this direction.

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