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Novelties in pharmacological management of cardiopulmonary resuscitation

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Abstract

Purpose of review—The ultimate goal of cardiopulmonary resuscitation is long-term neurologically intact survival. Despite numerous well designed studies, the medications currently used in advanced cardiac life support have not demonstrated success in this regard. This review describes the novel therapeutics under investigation to improve functional recovery and survival.

Recent findings—Whereas current medications focus on achieving return of spontaneous circulation and improved hemodynamics, novel therapies currently in development are focused on improving cellular survival and function by preventing metabolic derangement, protecting mitochondria, and preventing cell death caused by cardiac arrest. Improved cardiac and neurologic function and survival benefits have been observed using animal models of cardiopulmonary arrest.

Summary—Although substantial data have shown benefits using robust animal models, further human studies are necessary to investigate the potential long-term benefits of these therapies.

Keywords

advanced cardiac life support; cardiac arrest; cardiopulmonary resuscitation; mitochondrial protection; reperfusion injury

INTRODUCTION

Despite advances in medical science, the mortality from out-of-hospital cardiac arrest (OHCA) has remained stable for over 30 years with rates of survival to hospital discharge with good neurologic function of 5–8% [1[■],2–4]. These low survival rates have led to research exploring alternative pathways relevant to resuscitation. Each therapy is designed to counter the damaging effects of at least one mode of injury during cardiopulmonary arrest

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Conflicts of interest

J.A.B. MD/PhD has no conflicts of interest.

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(Fig. 1). These injuries occur in fundamental stages: the initial ischemic injury with hypoxemia, decreased ATP production, and acidosis; additional ischemic injury and mild reperfusion injury incurred during low blood flow states such as that provided by cardiopulmonary resuscitation (CPR); electrical injury caused by defibrillation; and reperfusion injury which occurs once return of spontaneous circulation (ROSC) is achieved. In contrast to current treatment algorithms, which focus on establishing ROSC and maintaining hemodynamic stability by maintaining adequate blood pressure thereby limiting ischemic injury, recent research efforts have focused on therapies that reduce injury caused by ischemia and subsequent reperfusion at the cellular level, thereby maintaining organ function and improving neurologic recovery. The following discussion will begin with a brief summary of current treatments followed by discussion of novel therapies addressing reperfusion injury and mitochondrial function.

CURRENT PHARMACOTHERAPY

Like CPR and defibrillation, current use of medications also focuses on establishing ROSC and maintaining hemodynamic stability by maintaining sinus rhythm and adequate blood pressure. However, the effect of these medications on survival and neurological recovery remains unclear.

Epinephrine

Epinephrine has been the mainstay of pharmacotherapy for cardiopulmonary arrest since the 1940s with the ability to increase systemic blood pressure via α 1-adrenergic receptors [5], increase coronary and cerebral perfusion [6,7], and increase rate of ROSC [1■]. However, no significant evidence has shown improved survival to hospital discharge, 1-month survival, or post-resuscitation neurological function with use of epinephrine. Further, animal studies have demonstrated reduced microcirculatory blood flow including cerebral perfusion [8], increased myocardial oxygen consumption [9], and increased ventricular ectopy [10] which may worsen postresuscitation myocardial dysfunction [11]. These effects are likely related to stimulation of β -adrenergic receptors. Stimulation of β -adrenergic receptors has also been implicated in myocardial calcium overload caused by release of calcium from the sarcoplasmic reticulum [12]. This may lead to electrical instability as well as possible apoptosis. These effects of the β -adrenergic receptors may explain the limited clinical benefit observed.

The effects of epinephrine were assessed with a randomized placebo-controlled trial with patients suffering OHCA [13]. The rates of ROSC were significantly higher in the epinephrine group; however, there was no difference in survival to hospital discharge or neurological outcome. Registry data go further to suggest that patients who receive epinephrine have decreased survival and neurological outcomes [1■]. Similar results were also found in a post-hoc analysis investigating the effects of epinephrine in patients with OHCA enrolled in a randomized trial testing prehospital IV placement [14■]. Patients receiving epinephrine had a higher rate of survival to hospital admission, but a reduced rate of survival to hospital discharge and a reduced rate of favorable neurological function at discharge. Currently, the role of epinephrine is considered to be limited to achieving ROSC and efforts should be made to limit the total amount and number of doses delivered.

Vasopressin

Vasopressin was tested as an adjunctive treatment to epinephrine as its actions proceed through vasopressin receptors thereby potentiating the effects of endogenous catecholamines. Multiple studies using porcine models of ventricular fibrillation arrest found significantly increased coronary and cerebral perfusion pressures, cerebral blood flow, and post-resuscitation mean arterial pressure with alternating doses of epinephrine and vasopressin [15,16]. However, rates of ROSC and neurological recovery were similar as were post-resuscitation cardiac output, ventricular dysrhythmia, lactic acid production, and troponin-I levels.

Human trials have provided mixed results with some studies demonstrating improved rates of ROSC [17] and hospital discharge rates [18] with the use of combination vasopressin/epinephrine therapy, whereas others observed no significant differences in rates of ROSC, hospital discharge, survival, or neurologic recovery [19,20]. Two meta-analyses concluded that there was no clear benefit of using vasopressin in combination with epinephrine compared to epinephrine alone [21,22]. The role of potent vasoconstrictors during CPR, although widely accepted as the standard of care, needs to be redefined.

Amiodarone

As significant as maintaining blood pressure with vasopressor agents as discussed, is maintaining a perfusing rhythm. In the case of ventricular tachycardia and ventricular fibrillation, amiodarone is the most commonly used medication to establish and maintain sinus rhythm. Despite this, no trial has yet shown long-term survival benefit with use of amiodarone. Multiple trials have shown improved rate of survival to hospital admission [23,24]. The Resuscitation Outcomes Consortium is currently conducting a study involving 25 000 patients testing the effect of amiodarone on neurologically intact survival to hospital discharge compared to lidocaine and placebo. This large study will provide more definitive insight into this difficult question.

NOVEL THERAPIES

Although current therapies used to treat cardiopulmonary arrest have been designed and used clinically to maintain hemodynamic stability, the next generation of therapies instead focuses on cellular survival and function with the purpose of increasing long-term survival and end organ viability and functional recovery. They do this by preventing one or more stages of injury occurring during cardiopulmonary arrest.

β -blockers

The questionable effects of epinephrine on long-term survival, as discussed above, are predominantly related to stimulation of the β -adrenergic receptors. Importantly, cardiopulmonary arrest triggers intense activation of endogenous sympathetic pathways resulting in stimulation of β -adrenergic receptors even without addition of exogenous epinephrine [25]. However, the circulating levels of endogenous epinephrine are magnitudes lower than those delivered exogenously.

Use of β -blockers in CPR was first investigated in 1994 with use of propranolol demonstrating improved coronary perfusion pressures during CPR without impact on defibrillation success or ventricular function [26]. Since then, various β -blockers have been tested with esmolol [25], atenolol [27], carvedilol [28], and metoprolol [29] showing improvement in the rate of ROSC, coronary perfusion pressure, cardiac and neurologic function, and survival. However, not all β -blockers have been beneficial with labetalol failing to improve rates of ROSC [29]. The reason for this difference is unknown though the additional β_2 -adrenergic blockade, α_1 -adrenergic blockade, and mild sympathomimetic activity of labetalol may all participate.

Human studies of β -adrenergic receptor blockers in cardiac arrest are lacking. Multiple case reports and case series are available. A single randomized trial was conducted including 49 patients with electrical storm (multiple recurrent ventricular fibrillation episodes) related to recent myocardial infarction [30]. The patients were randomized to sympathetic blockade or ACLS guideline-derived antiarrhythmic therapy. Of the patients in the sympathetic blockade group, 78% received esmolol or propranolol, whereas the others had ganglionic blockade. Survival at 1 week and 1 year was improved with sympathetic blockade as compared to antiarrhythmic therapy. Further rigorous study in human populations is necessary to fully understand the role for β -blockers in the treatment of cardiopulmonary arrest.

Cardioprotective vasodilator therapy

Myocardial energy balance is disturbed during cardiopulmonary arrest due to decreased coronary perfusion in conjunction with increased myocardial oxygen demand induced by endogenous catecholamine release as well as exogenous epinephrine use. In parallel, decreased cerebral perfusion and reduced microcirculatory blood flow induced by catecholamines likely influences neurologic recovery.

Sodium nitroprusside

Sodium nitroprusside (SNP) is a nitric oxide donor and potent vasodilator. In an effort to restore myocardial and cerebral energy balance with improved perfusion, a series of studies [31,32,33–35] using a porcine model of ventricular fibrillation postulated that infusion of SNP during CPR would improve blood flow and perfusion of vital organs thereby improving resuscitation and recovery. Carotid blood flow, end-tidal CO_2 , and arterial pH were all increased with SNP treatment. Rates of ROSC, 24 h survival, recovery of cardiac function, and neurologic recovery were also increased in the SNP group. The effect of SNP is closely related to the mechanical CPR platform. The CPR method used with SNP needs to redirect blood toward the vital organs and decrease peripheral blood flow. As such SNP has only improved outcomes in combination with active compression decompression CPR, an inspiratory impedance threshold device and abdominal binding. The combination described is called SNP-‘enhanced’ CPR (SNPeCPR). SNP during standard CPR does not offer any observed advantage. Human studies are necessary to further understand the potential for SNP use in CPR.

Adenosine

Adenosine is an arteriolar vasodilator while also preventing platelet aggregation, increasing endothelial and myocardial ATP stores, and inhibiting neutrophil function thereby decreasing reactive oxygen species. These attributes were hypothesized to prevent endothelial damage, which is known to occur during ischemia and improve myocardial microcirculation. The first studies used a coronary occlusion model demonstrating reduced infarct size with increased epicardial and endocardial blood flow in animals treated with intracoronary adenosine [36,37]. Neutrophil infiltration and endothelial damage were reduced, whereas endothelial-dependent and independent vasodilatory reserve, coronary blood flow, and coronary vascular resistance were improved [38].

Human studies of adenosine have also been conducted in patients undergoing reperfusion therapy during ST-segment elevation myocardial infarction (STEMI). The Acute Myocardial Infarction Study of Adenosine-II trial showed reduction in infarct size with adenosine infusion which correlated with reduced clinical events such as 1-month mortality, 6-month mortality, and composite endpoint of death, new congestive heart failure (CHF), or rehospitalization for CHF when patients had reperfusion within 3 h of symptom onset [39].

Studies testing adenosine in the setting of cardiopulmonary arrest are limited. Adenosine has been tested as a component of cardioplegia to replace high potassium levels and has been found to afford similar cardioprotection [40]. In a porcine model of ventricular fibrillation arrest involving 15 min of untreated ventricular fibrillation, adenosine was added to SNPeCPR-treated animals. Adenosine-treated SNPeCPR animals had further increased cerebral blood flow after 5 min of CPR [41]. Arterial blood pressure and coronary perfusion pressure were similar. It appeared that the addition of adenosine improved cardiac function without providing further neurologic benefit compared to SNPeCPR alone after cardiac arrest. All animals treated with SNPeCPR and adenosine had better left ventricular (LV) function and neurological intact survival compared to controls treated with standard CPR. Unfortunately the individual effect of adenosine cannot be teased out from the current study.

Mitochondrial protection

Although there are multiple mechanisms of injury during ischemia and subsequent reperfusion, one of the most detrimental to cellular function involves damage to the mitochondria resulting in initiation of necrosis and apoptosis [42–45]. The process by which reperfusion injury is prevented after the ischemic event has begun is called postconditioning. Multiple medications have been implicated in the process of postconditioning though they converge on a few signaling pathways which inhibit opening of the mitochondrial permeability transition pore (mPTP). The best-described pathway is the reperfusion injury salvage kinase pathway which involves phosphatidylinositol 3-kinase (PI3K) or ERK signaling cascades. Multiple ligands for G-protein-coupled receptors act through this pathway including adenosine.

Nitric oxide

Nitric oxide is involved in multiple aspects of the postconditioning process. Nitric oxide constitutes the first step in the survivor activating factor enhancement pathway, which is the

primary alternate pathway inhibiting mitochondria-induced cell death. It does this by activating TNF- α which activates the JAK/STAT pathway. Nitric oxide also acts as an effector molecule for the PI3K pathway. PI3K results in activation of endothelial nitric oxide synthase (eNOS), increased nitric oxide production, and subsequent activation of cyclic guanosine monophosphate and protein kinase G which results in decreased calcium release from the sarcoplasmic reticulum thereby decreasing the overall calcium load affecting the mitochondria leading to reduced mPTP opening. As a nitric oxide donor, SNP may enhance activation of this pathway.

Nitrite

A precursor for NO, nitrite has been shown to increase post-arrest left ventricular ejection fraction, decrease histopathological evidence of neuronal injury, increase survival, and improve neurologic function in rodent models of cardiac arrest [46,47]. These effects were attributed to reversible inhibition of mitochondrial complex I which prevented production of reactive oxygen species during the immediate reperfusion injury while allowing recovery as the nitrite was metabolized. Of note, conversion of nitrite to nitric oxide is dependent on pH and deoxygenation providing for preferential conversion in areas of ischemia. Phase I studies have been conducted to ensure safety in a human population including survivors of cardiac arrest [47]. Further trials are planned.

Opioids

Opioids have been shown to provide postconditioning in animal models through PI3K-glycogen synthase kinase 3β signaling [48]. Infarct size and biochemical and histological markers of apoptosis were decreased with sufentanil infusion in a rat model of myocardial infarction [49]. No human trials have been completed which confirm this finding, but opioids are commonly used for sedation in the setting of cardiac arrest.

Cyclosporine

Opening of the mPTP is mediated by an interaction between the pore and a matrix protein, cyclophilin D. This interaction is calcium-dependent and is inhibited by cyclosporine interacting with cyclophilin-D. Multiple studies using porcine models of cardiogenic shock have shown improved cardiac function, improved mitochondrial function, reduced myocardial ischemia, and decreased apoptosis with cyclosporine treatment [50,51,52]. Human studies have also been underway to evaluate the potential benefit of cyclosporine treatment in myocardial infarction. Cardiac biomarkers and infarct size were reduced in STEMI patient treated with cyclosporine [53,54]. Further studies testing cyclosporine in cardiac arrest are necessary.

Decreasing calcium overload: cariporide

Increased cytosolic calcium load can lead to mitochondrial destruction and cell death, but it may also lead to life-threatening arrhythmia including ventricular fibrillation. Release of calcium from the sarcoplasmic reticulum, mediated by the $\text{Na}^+/\text{Ca}^{2+}$ exchange pump, is an important source of intracellular calcium during ischemia. This release can be exacerbated by elevated activity of a sarcolemmal Na^+/H^+ pump. Cariporide is a selective inhibitor of

the sarcolemmal Na^+/H^+ pump. Pigs treated with cariporide during ventricular fibrillation arrest had reduced ectopy, improved cardiac function, and higher mean aortic pressure after ROSC compared to placebo [55,56]. Infarct size and postischemic LV function have also been improved using cariporide in a porcine model of coronary occlusion [57,58].

Inhaled anesthetics

For the purposes of resuscitation, the ability to deliver inhaled compounds rapidly without intravenous access makes them ideal medications.

Sevoflurane

The effects of volatile anesthetics on cardiac function have been studied for decades. Animal studies suggested that sevoflurane and isoflurane had mild dose-dependent negative inotropic effects as compared to the much more prominent effects of halothane [59]. It was believed that these differences arose from differential effects on inward calcium currents and the sarcoplasmic reticulum. When tested in a porcine model of ventricular fibrillation arrest, sevoflurane treatment reduced release of cardiac biomarkers, reduced apoptosis, and improved LV systolic and diastolic function. No differences in neurologic function were noted. Further study is necessary to understand the role of sevoflurane in postconditioning as well as the mechanism for any effect.

Xenon

Xenon is an inert noble gas, which is known to interact with biological systems. It causes unconsciousness when inhaled at a concentration greater than 45% and is known to inhibit *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system. Multiple reports of neurologic protection have been written including patients who have endured stroke and traumatic brain injury. It is thought to exert these effects through inhibition of protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and NMDA receptors, which are known to play a role in ischemic neuronal death. In a porcine model of ventricular fibrillation arrest, xenon treatment reduced the presence of neuronal necrosis and perivascular inflammation [60]. The xenon-treated animals had more rapid neurologic recovery post-ROSC though the difference resolved by day 4. No difference in hemodynamics or lactic acid levels was noted.

CONCLUSION

Despite our enhanced understanding of the pathophysiology of ischemia and reperfusion injuries, very little progress has been made in the improvement of neurologically intact survival after cardiopulmonary arrest. A shift is now taking place, from short-term goals of ROSC and hemodynamic stability, which remain fundamental to successful resuscitation, to improving neurologic and cardiac function post-ROSC. With that shift has come the necessity for research into cellular therapies that can achieve these goals by applying our understanding of pathophysiology while questioning our current treatment strategies.

REFERENCES AND RECOMMENDED READING

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

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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KEY POINTS

- Current ACLS therapies reproducibly improve rates of ROSC, but fail to improve neurologically intact survival.
- Novel therapies improve cellular survival and function by preventing the metabolic derangement, protecting mitochondria, and preventing cell death caused by cardiac arrest.
- Ischemic postconditioning has improved cardiac and neurological function as well as survival in animal models of cardiac arrest; however, further human trials are necessary to support their role in cardiopulmonary resuscitation.

FIGURE 1.

Phases of injury in cardiopulmonary arrest with potential therapies. There are four distinct stages of injury during cardiopulmonary arrest and resuscitation shown here. Each has a distinct mechanism of injury and various therapies directed toward prevention of the injury.