Mini-review

Emerging pharmaceutical therapies in cardiopulmonary resuscitation and post-resuscitation syndrome

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ABSTRACT

Objective: The medication used in cardiopulmonary resuscitation (CPR) has by no means yielded the expected prognostic benefit. This review focuses on drugs that are currently under investigation as part of novel therapeutic strategies in CPR and post-resuscitation care.

Data sources: The main categories of drugs under investigation were identified in position papers regarding gaps in scientific knowledge and research priorities in CPR. The electronic bases of Medline via PubMed and the ClinicalTrials.gov registry were searched. Research terms were identified using the MESH database and were combined thereafter. Initial search terms were “cardiac arrest”, “cardiopulmonary resuscitation”, “post-cardiac arrest syndrome” combined with “drugs” and also the names of pharmaceutical categories and related drugs.

Results: Novel pharmaceutical approaches rely on a better understanding of the pathophysiology of cardiac arrest and post-resuscitation syndrome. Some medications are targeted primarily towards enhancing the return of spontaneous circulation and increasing survival rates, while others mostly aim at the attenuation of post-arrest myocardial and neurological impairment. Only a few of these therapies are currently being evaluated for clinical use. Despite the remarkable variability in study quality and success in achieving therapeutic targets, results for most therapies seem encouraging and support the continuation of research.

Conclusion: New pharmaceutical modalities are being investigated for future use in CPR. Currently, none has been unequivocally accepted for clinical use, while only a few of them are undergoing clinical testing. This research is likely to continue, in view of the unsatisfactory results of current pharmaceutical therapies and the encouraging results of preliminary studies.

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Despite recent advances in cardiopulmonary resuscitation (CPR) survival rates after cardiac arrest (CA) are not yet satisfactory. Reported rates of return of spontaneous circulation (ROSC) seldom exceed 30% for in-hospital CA and only 15% of these patients survive neurologically intact.1 Moreover, survival to hospital discharge in most emergency medical systems has remained below 5% for out-of-hospital cardiac arrest (OHCA).

Expectations for a better outcome for victims of CA rely mostly on the implementation of public access defibrillation programs for OHCA and the generalised use of therapeutic hypothermia. Routine use of medication during CPR remains empirical without proven efficacy. A recent randomised controlled trial failed to show any benefit of drug administration on patient survival.2

For the moment the pharmaceutical counterpart of therapeutic hypothermia is lacking. However, considerable research is going on in search of medication that would truly benefit CA victims. This review is focused on drugs that were recently tested for routine use in CPR, and also drugs that are in earlier stages of investigation but have the potential to offer new therapeutic strategies in CPR and post-resuscitation care in the future.

1. Vasopressor drugs

Despite a lack of sound documentation, adrenaline is administered during CPR in an effort to redistribute cardiac output in favour of vital organs, augment coronary perfusion pressure and increase rates of ROSC. Noradrenaline and phenylephrine are not superior to adrenaline.3,4 Vasopressin is a potent vasoconstrictor that activates V1α receptors on arterial smooth muscle cells. It remains active during tissue hypoxia and acidosis and lacks the drawbacks of β-adrenergic stimulation. Animal studies suggested that vasopressin might be more effective than adrenaline in improving vital organ perfusion during CPR and can also maintain coronary perfusion pressure above the threshold needed for successful defibrillation.5 A small randomised human trial also yielded encouraging results,6 but 2 large randomised controlled trials failed to show any overall benefit from vasopressin use in terms of survival or mental performance of survivors of in-hospital7 and OHCA. A survival benefit was evident, however, for OHCA patients with asystole.8 Vasopressin is recommended by the American Heart Association9 as an alternative to the first two doses of adrenaline, but it was not included in the ERC guidelines.1 Repeated doses of vasopressin, given to OHCA patients, were not better than adrenaline alone for improving survival (Table 1).10

The combination of vasopressin and adrenaline also failed to improve OHCA patient outcomes over adrenaline alone.11 In this study VF and survival rates were, however, unusually low which challenges generalizability of results.

It is unclear why vasopressin failed to show an unequivocal benefit in humans. Delayed onset of action, prolonged vasconstriction/increased afterload on the heart, negative inotropic effect and...

### Table 1

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coronary vasoconstriction are possible components of the explanation. Trials testing the combination of vasopressin and adrenaline in ICU paediatric patients and the simultaneous administration of vasopressin, adrenaline and methylprednisolone to in-hospital CA patients are under way to investigate other aspects of vasopressin use in CPR.

2. Corticosteroids

Haemodynamic instability is common post-ROSC. Cortisol levels often remain low or rise insufficiently to match patient needs during haemodynamic stress. This relative adrenal insufficiency is common, occurring in 43–52% of patients post-ROSC, but often remains undetected.12

Most studies suggest that serum cortisol levels are higher in survivors of CA,13 and patients who fail to increase cortisol levels often die due to refractory post-CA shock. There are, however, reports that ACTH and free cortisol levels are higher sol levels often die due to refractory post-CA shock. There are, however, reports that ACTH and free cortisol levels are higher in non-survivors of CA, indicating that persistent hypotension and fatal cerebral damage may cause greater activation of the pituitary–adrenal axis.14 This discrepancy possibly reflects differences in the prevalence and severity of circulatory shock and other existing comorbidities among the populations of these small studies. It also underlines knowledge gaps regarding factors that may affect the pituitary–adrenal reaction to stress post-ROSC.

Post-resuscitation disease shares common features with sepsis, such as reversible myocardial dysfunction, vasodilatation, coagulation disorders and increase of pro-inflammatory mediators (IL-1ra, 6, 8, 10, TNFa).15 It is possible that tissue hypoperfusion and high levels of inflammatory cytokines post-CA may lead to derangement of the pituitary–adrenal axis.

In a prospective, non-randomised, open-label trial,16 hydrocortisone administration was related with a significantly higher rate of ROSC, but there was no treatment benefit in terms of short-term survival. In 100 in-hospital CA patients the combination of vasopressin and adrenaline plus methylprednisolone during CPR followed by hydrocortisone, when post-ROSC shock was present, was compared to adrenaline and placebo. Combination therapy increased ROSC and survival to hospital discharge.17

Both inhibitory and neutral effects of therapeutic hypothermia on the pituitary–adrenal axis have been reported.14,18 Trials testing the effects of hydrocortisone administration in OHCA victims and in patients in post-resuscitation refractory shock are in progress and hopefully will cover some knowledge gaps in the field.

3. β-Blockers

Endogenous catecholamines are often markedly elevated during CA, and this may result in myocardial damage, through stimulation of β-adrenergic receptors and the resulting increase of myocardium oxygen demand both in the fibrillating heart19 and post-ROSC. These effects are linked to myocardial dysfunction and the induction of malignant arrhythmias in patients surviving CA.

β-Adrenergic inhibition was first tested as a means of myocardial protection in acute myocardial infarction. In these patients β-blockers significantly reduced the incidence of VF and recurrent ischaemia but may be associated with haemodynamic compromise or shock.20 By extrapolation, β-blockade might also exhibit similar effects during ischaemia/reperfusion in the peri-arrest period. In animal VF models esmolol, compared to placebo, improved ROSC rate and short-term survival, minimised the number of shocks needed and ameliorated post-resuscitation myocardial dysfunction.21 Esmolol may also reduce VF inducibility by modulating the restitution of activation-recovery intervals and affecting intracellular calcium handling.22 In animal VF models atenolol and propranolol, given during CPR in conjunction with adrenaline, made resuscitation more effective and improved ROSC rate in comparison to adrenaline alone.23

Apart from stimulating β-adrenergic receptors, exogenous adrenaline is also a powerful a1- and a2-adrenergic receptor stimulator. Activation of a1-adrenergic receptors in the heart leads to positive inotropic action, increased myocardial oxygen consumption and coronary vasoconstriction.24 a2-Adrenergic receptors are found in arterial smooth muscle and are responsible for vasoconstriction caused by catecholamines. Thus adrenaline is administered in CA victims mainly for its action on a2 adrenal receptors, while there is increasing scepticism about its concurrent actions on β- and a1-receptors.

In a porcine VF model, simultaneous administration of a1-blocker prazosin, β-blocker propranolol, and adrenaline improved post-resuscitation cardiac output and neurological recovery when compared to adrenaline alone.25 Carvedilol, a β-blocker with a1-blocking actions, showed similar outcomes in a rat VF model when it was added to adrenaline.26 In animal VF models, a-methylnoradrenaline, a selective a2-adrenergic agonist, showed similar efficacy but better post-ROSC ventricular function than adrenaline.27 In a VF arrest model in dogs, concurrent a2-stimulation and β-blockade using phenylephrine and propranolol during CPR resulted in higher and more sustained coronary perfusion pressures compared to adrenaline or phenylephrine alone.28

There is no convincing evidence for beneficial effects of β-blockers in human CA. There are, however, a few retrospective reports indicating a beneficial effect on survival of CA patients when β-blockers were administered as part of the immediate in-hospital post-resuscitation care in OHCA, or when β-blockers were included in patients’ pre-arrest medications.29,30 Preliminary human studies are needed to facilitate research into the safety and efficacy of β-blockers in the treatment of CA.

4. Sodium–hydrogen exchanger inhibitors

The Na+/H+ exchanger (NHE) is a transmembrane pump that is found in most tissues and plays a pivotal role in the regulation of intracellular pH by removing H+ in exchange for Na+ entry into the cells.31 Of the 5 isoforms of NHE, isoform 1 (NHE1) is cardiосpecific. Acidosis and ischaemia are the most powerful stimuli of NHE1. Yet, NHE1 remains activated not only during CA, but also during reperfusion. The low blood flow at the beginning of reperfusion cannot reverse ischaemia but can wash out extracellular H+, preserving the concentration gradient across the sarcolemma and thus keeping the pump activated.32 Na+ accumulation in the normoxic cardiac cell is prevented by Na+/K+-ATPase, which removes Na+ from the intracellular space. Under conditions of ischaemia and severe acidosis Na+/K+-ATPase is inactivated, leading to an increase of cytosolic Na+ which in turn triggers Ca2+ entry into cells through an Na+/Ca2+ sarcolemmal pump. Intracellular Ca2+ accumulation appears to be the main mechanism of cell injury due to Na+ overload. Na+ extrusion from the intracellular space is energy dependent and may lead to depletion of intracellular ATP.

Metabolic derangement during ischaemia may eventually lead to apoptosis and ischaemic contracture.33 The latter may be caused by either inadequate ATP production for the dissociation of the actin–myosin complex, or inadequate energy to restore resting cytosolic Ca2+ levels.34 Fall of tissue ATP below a critical level has been proposed as an initiating factor for ischaemic contracture, while the importance of an inadequate rate of glycolytic ATP production has also been emphasised. Ischaemic contracture is characterised by progressive thickening of the left ventricular...
wall and a severe reduction in ventricular cavity size. Diastolic properties and filling of ventricular cavities are therefore compromised and cardiac output is diminished. In addition, Na⁺ and Ca²⁺ overload causes shortening of the action potential during ischaemia/reperfusion, thus triggering recurrent malignant ventricular arrhythmias post-ROSC. NHE proteins are also involved in intracellular pH and volume regulation and may influence neurotransmission. NHE1 has also been linked to brain cell damage during metabolic stress, through disruption of Na⁺ and Ca²⁺ homeostasis.

In view of the role of NHE in mediating the detrimental effects of ischaemia/reperfusion at the cellular level, inhibition of this exchanger has been studied as a potential means of myocardial protection and arrhythmia inhibition in the peri-arrest period. Cariporide, a selective NHE1 inhibitor, yields the greatest amount of evidence. In animal models it has been effective in ameliorating peri-arrest arrhythmias by preventing shortening of the action potential post arrest. It has also been found effective for ameliorating ischaemic contracture and transient post-arrest myocardial dysfunction, probably by limiting Na⁺-induced Ca²⁺ overload.

Cariporide was used in two phase III studies for myocardial protection during coronary artery bypass graft surgery. Both of them showed a decrease in MI rates, while an increase in short-term mortality in the cariporide group was found in the EXPEDITION study, which associated with an increase in cerebrovascular events. The beneficial effects were evident at 6 months in both studies, while the difference in mortality was no longer significant.

5. Erythropoietin (Epo)

Besides its action on erythroid progenitor cells, Epo has a protective role against ischaemia/reperfusion injury in many tissues, including myocardium and brain. When it binds to its receptor, Epo triggers a series of phosphorylations of intracellular protein kinases, such as JAK2 and PI3K, leading to activation of protein kinase Akt, which in turn orchestrates the inhibition of cellular apoptotic mechanisms. Several experimental studies have shown the cardioprotective actions of Epo during CA. In a rat model of asphyxia-induced CA, intravenous Epo improved systolic and diastolic ventricular indices, as well as short-term survival, compared to placebo when administered 3 min post-ROSC. In this study there was no significant difference in neurological scores between the two groups and it was shown that the effects of Epo were driven by activation of the Akt signaling pathway.

In a rat VF-arrest model, Singh et al. tried to clarify the most appropriate timing of Epo administration during CA. Epo was more effective when given at the time of resuscitation (compared to 15 min before VF induction), resulting in higher coronary perfusion pressures for a given chest compression depth during resuscitation and in a significantly higher mean aortic pressure throughout the post-resuscitation interval. In a recent study of asphyxia-induced CA in rats, a single iv bolus dose of Epo administered 15 min before CA increased ROSC rate and short-term survival, with smaller dose of adrenaline needed during CPR, when compared to control rats.

In animals Epo has shown a neuroprotective effect during cerebral hypoxia-ischaemia, reducing cerebral infarct volume and increasing neuronal survival and ischaemic tolerance. These promising results brought about some clinical trials. The neuroprotective action of Epo was tested in OHCA patients. In a matched control study by Cariou et al., Epo-alpha (40,000 IU, followed by same dose every 12 h for the first 48 h) was administered after stable ROSC in OHCA patients and compared to placebo, while all the patients were admitted to the ICU and treated by mild hypothermia. After 28 days there was a trend towards better neurological recovery in the Epo-treated group, which never reached statistical significance, and there was no difference in terms of survival. Thrombocytosis occurred in 15% of patients in the Epo-group, and was related with one case of arterial vascular thrombosis.

Recently, Grmec et al. were the first to report Epo effects during CPR. In this study, an iv push of 90,000 IU Epo was given to OHCA patients within 2 min of EMS arrival on the scene. The Epo group, when compared to placebo and matched, historic controls, was associated with more effective chest compressions leading to higher ROSC rate, 24-h survival and survival to hospital discharge. These promising results were, however, obscured by serious methodological flaws, as the study design was abandoned in the interim and drugs were given in a non-randomised and open fashion allowing for various sources of bias.

Several clinical trials are in progress. A large, randomised, controlled, phase III trial in France will investigate the possible neuroprotective role of Epo-alpha in comatose survivors of CA up to 60 days after ROSC, while the hypothesis that Epo could facilitate brain recovery in ICU patients with traumatic brain injury will be assessed in a randomised trial in Australia and New Zealand.

6. Inotropes

Inotropes are currently recommended in post-CA syndrome for treatment of myocardial dysfunction, despite the fear of aggravation of focal ischaemia and dependency.

Dobutamine is effective in mitigating post-ROSC myocardial dysfunction, but as a result of its β-adrenergic effects it increases myocardium oxygen demands. Levosimendan, a calcium-sensitising inotropic drug, lacks β-adrenergic effects and does not increase intracellular calcium. It exerts its action through two mechanisms: (a) it stabilises the calcium-bound conformation of troponin C, eliminating its inhibitory effect on actin–myosin binding and increasing the life span of their cross bridges; and (b) it opens ATP-sensitive potassium channels in plasma membrane, promotes arterial vasodilation and mimics ‘ischaemic preconditioning’, making the myocardium more resistant to ischaemia/reperfusion injury.

Administered 10 min post-ROSC in rats, both levosimendan and dobutamine improved myocardial function, but levosimendan also increased the duration of post-resuscitation survival. In a swine VF model levosimendan achieved significantly better left ventricular systolic function post-ROSC than dobutamine or placebo.

In a pig CPR model, levosimendan plus adrenaline demonstrated enhancement of ROSC rate, coronary perfusion pressure and brain regional oxygen saturation, in comparison to adrenaline plus placebo. Despite the vasodilatory actions of levosimendan, hypotension was not affected, probably due to a concurrent increase in cardiac output. In another piglet VF arrest model, levosimendan plus atenolol and adrenaline was compared to adrenaline plus atenolol and to adrenaline alone. The combination of levosimendan, atenolol and adrenaline increased post-ROSC cardiac output and 48 h survival and was accompanied by indirect evidence of less myocardial and brain damage. The authors attribute the neuroprotective action of levosimendan to its vasodilatory effects, possibly increasing brain perfusion. Animal studies have also reported a synergistic action of levosimendan and β-blockers in improving post-resuscitation myocardial function.

Nevertheless, trials in humans are needed to establish the role of levosimendan as an alternative inotropic drug.

7. δ-Opioid agonists

Myocardial hibernation is associated with down-regulation of myocardial metabolism and oxygen consumption, as well as protection of cardiomyocytes from ischaemic injury. Mammalian
hibernation seems to be the result of a cyclic variation of opiate-like compounds in serum. Activation of endogenous δ-opioid receptors in animals reduces the size of an infarction induced by myocardial ischaemia.55 In a rat CA model, the δ-opioid agonist pentazocine, administered after VF induction, dramatically reduced myocardial metabolism, ameliorated ventricular systolic and diastolic dysfunc-
tion, and increased post-resuscitation survival in comparison to the control group.56 The effects of pentazocine were offset by the concurrent administration of the opioid antagonist naloxone. In an isolated rat-heart model pentazocine was more effective in preventing myocardial dysfunction when administered before CA rather than during the reperfusion period.57

The synthetic δ-opioid receptor agonist β-Ala (2)-d-Leu (5) enkephalin (DADLE), has also been tested in CA.58 In an iso-
lated working rat-heart model, pharmacological activation of delta-opioid receptors using DADLE offered myocardial protection similar to that conferred by ischaemic preconditioning. However, the evidence for cardioprotection with DADLE was not uniform among species.55

8. Thrombolysis

Acute myocardial infarction and pulmonary embolism are the most frequent causes of OHCA. Thrombolytic therapy was intro-
duced into CPR research in the hope of removing obstructive clots from the pulmonary or coronary circulation and restor-
ing spontaneous circulation. Animal data supported the idea that thrombolytic therapy could prevent post-resuscitation no-reflow phenomena in the cerebral circulation, thus improving the neuro-
logical outcome.59

Initial reports coming from small case series, retrospective data, MI databases and historic control studies, yielded encouraging results.60

In the TROICA study tenecteplase was compared to placebo in patients with witnessed OHCA of presumed cardiac origin. The study was terminated prematurely, since no treatment benefit was expected if enrolment was completed. Moreover, thrombolysis increased the risk of intracranial bleeding.61

The study results have discouraged the routine use of throm-
bolysis therapy during CPR. Thereafter, only a few reports from retrospective cohorts of patients show possible benefits from thrombolytic therapy in certain subgroups of patients with pul-
monary embolism and STEMI.62,63

Thrombolytic therapy is indicated post-ROSC in patients with STEMI and no possibility for invasive reperfusion.48

9. Hypothermia

Mild therapeutic hypothermia (32-34 °C) is a well established neuroprotective treatment for comatose survivors of CA. Apart from several cooling devices, endogenous substances can cause hypothermia. Neurotensin is a tridecapeptide expressed in mammal brain and gastrointestinal tract that can pro-
duce hypothermia by downward shifting the temperature set point in the hypothalamus (‘regulated hypothermia’). Continuous intracerebroventricular infusion of neurotensin in rats led to a dose-dependent decrease of body temperature to 35–36 °C, last-
ing up to 12–24 h.64 These data may herald a new method for rapid on-site induction of hypothermia in patients resuscitated from CA.

10. ATP-sensitive potassium channel activators

ATP-sensitive potassium channels are located in the sar-
clemma of the cardiomyocyte (sKATP) and in mitochondrial membrane (mitoKATP). Animal studies have shown that activa-
tion of mitoKATP leads to protection of myocardial and brain cells from ischaemia and is related to ischaemic preconditioning. In ischaemic preconditioning, transient, brief exposures of the heart to ischaemia lead to a significant reduction in infarct size following subsequent exposure to lethal ischaemic stimuli. The mechanism of cardio- and neuroprotection has not been completely elucidated. It is considered that opening of mitoKATP leads to activation of protein kinase C, which in its turn limits reactive oxygen species (ROS) release, activates ROS scavengers, attenuates calcium influx in mitochondria and finally reduces cellular damage and death. In the heart, mitoKATP activation also leads to shortening of the action potential duration, and contributes to electrical stability and sup-
pression of triggered arrhythmias secondary to calcium-dependent after-depolarisations.65 The anti-arrhythmic effect of KATP opening is also corroborated by the finding that mutations of the KATP channels increase the risk for adrenergic atrial fibrillation.66 In the brain, activation protects the microcirculation and the blood–brain barrier against ischaemic stress. Hence, activation of the channels seems to be vital for adaptation to physiological and pathological stress.

In patients with heart failure, remodelling of the heart dis-
rupts KATP channel activity and leads to an improper response to ATP under conditions of hypoxia. At the same time, mutations of genes encoding for KATP components, such as SUR2A protein, have been discovered in patients with heart failure.67 Activators of mitoKATP can offer acute and delayed protection to myocardium and brain through different mechanisms (acute and delayed pre-
conditioning). In acute preconditioning KATP activation attenuates intracellular calcium influx and hence prevents mitochondrial swelling, while in delayed preconditioning activation leads to sus-
taght mitochondrial depolarisation, a decrease in ROS surge, and maintenance of ATP levels.68

Many KATP channel activators have been tried, such as nicor-
randil, pinacidil and BMS-191095, but the most potent of all seems to be diazoxide, an antihypertensive agent. Diazoxide is a selec-
tive mitoKATP channel activator and at the same time inhibits succinate dehydrogenase, which causes liberation of ROS indepen-
dent of mitoKATP opening. The effects of diazoxide on mitoKATP channels are blocked by 5-hydroxydecanoate (5-HD) and gliben-
clamide. Neuro- and cardioprotective effects of diazoxide have been shown in animal studies.69 Diazoxide has also shown card-
dioprotective actions when co-administered with cardioplegia in patients undergoing coronary artery bypass grafting, by preventing mitochondrial swelling and improving energetics and post-surgical contractile function.70 What still remains to be done is the complete clarification of the underlying mechanisms and the execution of clinical trials to establish the beneficial role of mitoKATP activators in humans, during and after CA.

11. Other drugs

This review covers some major axes relating to ongoing research into CPR, but is far from covering the entire spectrum. There have been other, albeit more isolated, attempts to test the effects of various medications, all seeking to enhance ROSC and keep VF reversible.71 while there is also ongoing research into myocardial and brain protection that might also affect CA research.72,73

12. Conclusions

New pharmaceutical strategies in CPR should address two major problems: making CPR more effective in achieving ROSC and at the same time offering protection to vital organs. This effort is a con-

coming treatments rely on expectations for possible benefits from the innovative use of long-standing therapies. Others look to a better understanding of the mechanisms underlying cell damage in the setting of ischaemia/reperfusion encountered in the peri-arrest period. The pathophysiological background of new therapeutic modalities has thus been formed, and elementary hypotheses have been tested successfully, in most cases in animal studies. It remains, however, to be seen whether any of them will successfully finish the course from animal studies to clinical practice.

Conflict of interest

No conflicts of interest to declare.

References


