

## CPR UPDATE

## Drugs in Resuscitation

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**KEY WORDS:** *cardiac arrest; advanced life support; resuscitation; resuscitation drugs; vasopressors; antiarrhythmics*

**ABBREVIATIONS**

CA = cardiac arrest  
CPR = cardiopulmonary resuscitation  
ROSC = return of spontaneous circulation  
VF = ventricular fibrillation  
VT = ventricular tachycardia

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## INTRODUCTION

Cardiac arrest (CA) is defined as the sudden cessation of spontaneous circulation and ventilation. Unfortunately, survival rates of both out of hospital and in hospital cardiac arrest remain low and merely unchanged over the last 30 years. Cardiopulmonary resuscitation (CPR) is an attempt to restore effective, spontaneous circulation and ventilation through a variety of interventions including early defibrillation, chest compressions, advanced airway management, pharmacological therapy and effective post-resuscitation treatment, once return of spontaneous circulation (ROSC) has been achieved. Both, European Resuscitation Council (ERC) and American Heart Association (AHA) have published detailed guidelines in an attempt to incorporate recent scientific advances in a variety of topics underpinning CPR.

The major concepts of these guidelines are the increased emphasis on high quality, minimally interrupted chest compressions of adequate rate and depth, avoidance of hyperventilation, early defibrillation for specific heart rhythms with minimization of the pre-shock pause and greater detail and importance on the treatment of the post-cardiac arrest syndrome.

Pharmacologic interventions continue to be a fundamental part of advanced life support, although there are no clinical data indicating that any drug improves long term survival after CA. In addition, there is inadequate evidence to define the optimal timing, dose or order for drug administration. The primary goal of pharmacologic therapy during CA is to facilitate restoration and maintenance of a perfusing and spontaneous rhythm. Vasopressors and antiarrhythmics are the main drug categories used in CPR algorithms. Novel pharmaceutical approaches are on the way, some of them being promising for future use.

**VASOPRESSORS**

To date no placebo controlled trial has shown that administration of any vasopressor agent, at any stage during management of CA increases the rate of neurologically intact survival to hospital discharge, although there is evidence that they may improve ROSC and short term survival. Epinephrine and vasopressin are the most studied vasopressors in CA.

*Epinephrine*

Epinephrine administration has been advocated in resuscitation for decades and forms a key component of published guidelines. Its use is based chiefly on animal studies while human trial evidence is scant. Epinephrine is a powerful agonist of both  $\alpha$ - and  $\beta$ -adrenergic receptors. It has been the vasopressor of choice because of its  $\alpha_2$ -adrenergic effects which cause systemic vasoconstriction, increase coronary and cerebral perfusion pressures and consequently the success of initial resuscitation. However, epinephrine has also  $\beta$ -adrenergic effects which increase myocardial oxygen consumption and the

severity of post-resuscitation myocardial dysfunction. The  $\beta$ -adrenergic effects of epinephrine also account for increases in ventricular ectopy and recurrence of ventricular tachycardia or fibrillation. In addition, epinephrine produces arteriovenous shunting through the lungs and therefore causes a very profound although transient reduction in the arterial oxygen content. The optimal dose of epinephrine is not known and there are no data supporting the use of repeated doses. Similarly, there are no data on the pharmacokinetics of epinephrine during CPR. The optimal duration of CPR and the number of shocks that should be given before administration of drugs is unknown. On the basis of expert consensus it is reasonable to consider administering 1mg dose of epinephrine IV/IO every 3 to 5 minutes during adult CA. ERC guidelines suggest that the first dose should be given after the third shock for VF/pulseless VT CA, once chest compressions have resumed, while AHA suggests that the first dose should be given after the second shock. Higher doses may be considered in special circumstances such as  $\beta$ -blocker or calcium channel blocker overdose or as indicated by hemodynamic monitoring. If the initial arrest rhythm is pulseless electrical activity (PEA) or asystole the administration of epinephrine is recommended as soon as vascular access is obtained.

#### *Vasopressin*

Vasopressin is a non-adrenergic naturally occurring vasoconstrictor that activates  $V_{1a}$  receptors on arterial smooth muscle cells causing peripheral, coronary and renal vasoconstriction. It remains active during tissue hypoxia and acidosis and lacks the drawbacks of  $\beta$ -adrenergic stimulation. Initial animal data suggested that vasopressin might be more effective than epinephrine. Optimism was fueled by animal studies demonstrating that vasopressin versus epinephrine increased blood flow in vital organs, improved cerebral oxygen delivery and increased the probability of restoring spontaneous circulation and neurologic outcome. However, vasopressin failed to show an equivocal benefit in humans. Delayed onset of action, prolonged vasoconstriction, increased heart afterload, negative inotropic effect and coronary vasoconstriction are possible components of the explanation. AHA recommends that one dose of vasopressin 40 IU IV/IO may replace the first or second dose of epinephrine in the treatment of VF/pulseless VT CA. Its use was not included in the ERC guidelines.

There are no alternative vasopressors or combination of vasopressors with proven survival benefit compared with epinephrine.

#### **ANTIARRHYTHMICS**

There is no evidence that any antiarrhythmic drug given routinely during human cardiac arrest increases survival to hospital discharge.

#### *Amiodarone*

Amiodarone is a diverse antiarrhythmic drug with complex electrophysiological and pharmacological profile. It has membrane stabilizing effects, increases duration of action potential and refractory period in atrial and ventricular myocardium and slows conduction in atrioventricular node and accessory pathways. It also exerts a mild negative inotropic action and causes peripheral vasodilation through non-competitive  $\alpha$ -blocking effects. Amiodarone may be considered for those who have refractory ventricular tachycardia (VT)/ventricular fibrillation(VF), defined as VF/VT not terminated by defibrillation, or VF/VT recurrence in out-of or in-hospital CA. Following three initial shocks, amiodarone improves the short term outcome of survival to hospital admission compared with placebo or lidocaine. Amiodarone also appears to improve the response to defibrillation when given to humans or animals with VF or haemodynamically unstable VT. In the clinical studies to date amiodarone was given when VF/VT persisted after at least three shocks. For these reasons and in the absence of any other data it can be considered for treatment of VF or pulseless VT unresponsive to shock delivery, CPR and vasopressors. An initial dose of 300mg I.V./I.O. can be followed by one dose of 150mg. Amiodarone should be available in all in-hospital and out-of-hospital cardiac arrests attended by emergency medical services.

#### *Lidocaine*

Lidocaine is an antiarrhythmic drug of long standing and widespread familiarity, which however has no proven short- or long term efficacy in CA. Comparative studies with amiodarone have proven the superiority of the first one and so lidocaine may be considered only when amiodarone is unavailable. The initial dose is 1-1.5mg/kg I.V. When VF pulseless VT persists additional doses of 0.5-0.75mg/kg I.V. push may be administered at 5 to 10 minute intervals to a maximum dose of 3mg/kg.

#### *Magnesium*

Magnesium is an emerging antiarrhythmic agent that can be best classified as a sodium/potassium pump agonist. It blocks atrial L and T type calcium channels, prolongs both atrial refractory period and conduction, inhibits potassium entry and suppresses ventricular after depolarisations. Observational studies showed that magnesium can facilitate termination of Torsades de Pointes (TdP) (irregular/polymorphic VT associated with prolonged QT interval). Magnesium is not likely to be effective in terminating irregular/polymorphic VT in patients with normal QT interval. The benefit of giving magnesium routinely during CA is unproven. Studies in adults and in out of hospital CA have failed to demonstrate an increase in the rate of ROSC when magnesium is given routinely during CPR. When VF/pulseless VT CA is associated with TdP providers may administer an I.V./I.O. bolus of

magnesium sulfate at a dose of 1-2gr peripherally over 1 to 2 minutes. Dose may be repeated in 10 to 15 minutes. Special situations where administration of magnesium is indicated are hypomagnesaemia and digitalis toxicity.

**OTHER DRUGS**

There is no convincing evidence that the routine use of other drugs during human CPR increases survival to hospital discharge.

*Atropine*

No prospective controlled clinical trial has examined the use of atropine in asystole or bradycardic PEA cardiac arrest. Available data suggest that routine use of atropine during PEA or asystole is unlikely to have a therapeutic benefit, because CA is usually due to primary myocardial pathology rather than excessive vagal tone. For these reason atropine has been removed from the cardiac arrest algorithm and its routine use is no longer recommended.

*Sodium bicarbonate*

Routine administration of sodium bicarbonate for treatment of in-hospital and out-of-hospital CA is not recommended. Tissue acidosis and resulting acidemia during CA and resuscitation are dynamic processes resulting from no blood flow during arrest and low blood flow during CPR. Restoration of oxygen content with appropriate ventilation and support of tissue perfusion with high quality chest compressions until ROSC is achieved are the mainstays of restoring acid-base balance during CA. Special circumstances where administration of sodium bicarbonate can be considered are CA associated with hyperkalaemia and tricyclic antidepressants overdose.

*Fibrinolysis*

Fibrinolytic therapy should be considered, as an empirical therapy, when CA is caused by proven or suspected acute pulmonary embolism. In these circumstances CPR should be performed for at least 60-90 minutes before termination of resuscitation attempts. Ongoing CPR is not a contraindication to fibrinolysis. Fibrinolytic therapy should not be routinely used in CA.

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**FUTURE PERSPECTIVES**

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**CORTICOSTEROIDS**

Early observational studies of the use of corticosteroids during CA suggested possible benefit. Recent study results indicate that hydrocortisone administration was related with significantly higher rate of ROSC but with no treatment benefit in terms of short term survival. There is insufficient evidence to support or refute the use of corticosteroids alone or in combination with other drugs during CA.

**B-BLOCKERS**

Beta-Blockade has been extensively studied in animal models of CPR (esmolol, atenolol). These studies not only suggest that beta-blockade could reduce myocardial oxygen requirements and the number of shocks necessary for defibrillation, but also improve post-resuscitation myocardial function, diminish arrhythmia recurrence and prolong survival. There are few case reports describing successful beta-blockade use in patients along with two prospective human studies suggesting that it could be safe and effectively used during human CA. Even though the existing literature points toward a beneficial effect of beta-blockade in patients presenting with CA due to VF/pulseless VT high quality human trials are still lacking to answer this question definitely.

**ERYTHROPOIETIN (EPO)**

Besides its action as the principal hematopoietic hormone Epo exhibits diverse cellular effects in non hematopoietic tissues. Due to its anti-apoptotic, anti-inflammatory, anti-oxidant properties, and its angiogenic action, Epo plays a role in neuroprotection and cardioprotection. Preliminary clinical data show that Epo given during CPR facilitates ROSC, ICU admission, 24hour-survival and hospital-survival as well as a trend towards better neurological recovery. Several clinical trials are in progress and hopefully will cover some knowledge gaps in the field. In this regard, Epo may represent a promising agent in the cardiac arrest setting.

**INOTROPES**

Inotropes are currently recommended in post-resuscitation syndrome for treatment of myocardial dysfunction, despite the fear of aggravation of focal ischaemia and dependency. Levosimendan is a calcium sensitizing inotroping drug that lacks  $\beta$ -adrenergic effects and does not increase intracellular calcium. Animal data demonstrate that administration of levosimendan plus epinephrine during CPR significantly improves initial resuscitation success and increases coronary perfusion pressure and brain regional oxygen saturation in comparison to adrenaline plus placebo. Animal studies have also reported a synergistic action of levosimendan and  **$\beta$ -blockers in improving** post-resuscitation myocardial function. Human trials are needed to establish the role of levosimendan in the CA setting.

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**OTHER AGENTS**

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Sodium-hydrogen exchange inhibitors (cariporide),  $\delta$ -opioid agonists (DADLE) and ATP sensitive potassium channel activators are new pharmaceutical modalities under investigation for future use in CPR, with preliminary and experimental data indicating a possible role.

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**CONCLUSION**

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Only a few drugs are indicated during the immediate management of CA and there is limited scientific evidence supporting their use. Drugs should be considered only after initial shocks have been delivered -if indicated- and chest compressions have been started. The evidence for the optimal timing and order of drug delivery and the optimal dose is limited. No

interruptions should be made in chest compressions in order to give drugs. Current practice still supports adrenaline as the primary vasopressor for the treatment of CA of all rhythms. Amiodarone is the antiarrhythmic drug of choice in the CA setting. Better understanding of the pathophysiology of the cardiac arrest has allowed the exploration of novel pharmaceutical approaches in most cases in animal studies. High quality, randomized controlled trials are still lacking in the area in order these to be safely implemented in human CA.