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PERSPECTIVES IN MEDICAL SCIENCES

Pharmacotherapy In Cardiopulmonary Resuscitation (CPR)

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Abstract: Cardiac arrest is defined as cessation of cardiac mechanical activity. Cardiopulmonary resuscitation (CPR) is an attempt to restore spontaneous circulation through several maneuvers and techniques. Although the two interventions, which are competent basic life support and prompt defibrillation, improve the survival rate, several adjuvant cardiac medication drugs are advocated to treat cardiac arrest during advanced cardiac life support. Since the introduction of modern CPR there have been many advances in the field of pharmacotherapy in CPR. Therefore, we aimed to summarise the cardiac medication drugs used for patients in ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) or non VF/VT in the practice of advanced cardiac life support. Towards achieving this aim, the effects and practical issues related to vasopressors, antiarrythmic agents and, others such as sodium bicarbonate, calcium, magnesium and atropine will be addressed in the scope of the recent updates in the literature.

Key Words: Advanced cardiac life support, Cardiopulmonary resuscitation (CPR), Drug therapy.

Introduction

Cardiac arrest is defined as cessation of cardiac mechanical activity. It is a clinical diagnosis, confirmed by unresponsiveness, absence of detectable pulse and apnea or agonal respirations. Cardiopulmonary resuscitation (CPR) is an attempt to restore spontaneous circulation through a broad range of maneuvers and techniques. Within 15 seconds of cardiac arrest, the patient loses consciousness, electroencephalogram becomes flat after 30 seconds, pupils dilate fully after 60 seconds and cerebral damage takes place within 90-300 seconds. Therefore, it is essential to act immediately as reversible damage can occur in a short time (1).

The range of activities and skills during Basic life support (BLS) has been expanded to include automated external defibrillators (AED) in addition to initial airway assessment, rescue breathing by small volumes of expired air ventilation and chest compressions. Uniform compression-ventilation ratio of 15:2 has been adopted for single as well as two rescues. AED have been made available to reduce time lapse in defibrillation. Defibrillators with biphasic current are also being used with several advantages. Standard manual chest compressions have been shown to be universally superior to alternative techniques (1-3).

In the present review pharmacotherapy in mainly two rhythm abnormalities such as VF/VT or nonVF/VT leading to cardiac arrest is addressed. Specific treatments for brady- and tachyarrhythmias are outside the scope of this article.

The reason for using vasoconstrictor agents in routine pharmacological efforts to increase coronary perfusion pressure is because of the insufficient release of endogenous vasoconstrictor caused by the neuroendocrine response to cardiac arrest. Vasopressors routinely used in CPR can be classified as adrenergic or nonadrenergic according to the mechanism of action (4).

Vasopressors

Vasopressor agents given during cardiac arrest aim to improve aortic diastolic pressure. Consequently, increases in coronary and cerebral perfusion pressures enhance both myocardial and cerebral blood flow and improve survival (4,5).

Adrenergic vasopressors

Adrenaline (epinephrine)

Adrenergic agonist; adrenaline (epinephrine) is routinely used to enhance cerebral and myocardial blood flow by preventing arterial collapse and by augmenting aortic diastolic pressure through alpha 1 and 2 receptors (1). Its alpha adrenergic receptor stimulating properties improves coronary perfusion pressure, while its potentially harmful beta adrenergic effects primarily beta 1 actions (inotropic and chronotropic) result in increases in myocardial oxygen consumption, in the incidence of ventricular arrythmias, and intrapulmonary shunting due to reduced hypoxic pulmonary vasoconstriction (4,5). Accordingly adrenaline increases myocardial lactate concentration and decreases myocardial ATP content (5). Although beta 2 actions are predominantly bronchodilatory, its stimulation in the myocardium further increases oxygen consumption during CPR and the severity of myocardial ischemic injury after successful CPR (5).

Adrenaline has not been shown to improve outcome (Class indeterminate) (Table 1 and 2), although it is one of the mainly used vasopressors in the practice of advanced cardiac life support (ACLS) (Figure) (3). Standard optimal dose recommendation for intravenous adrenaline is 1 mg (10 ml of in 10000 solution or 1 ml of 1 in 1000 solution) every 3-5 minutes according to ACLS guidelines (6, 7). However, in the majority of cases adrenaline did not appear to be administered according to current ACLS guidelines. The median interval between adrenaline doses during CPR was 6.5 min (7). Additionally, adrenaline is believed to stiffen the major vessels leading away from the heart, thus adding to the transmission of the raised intrathoracic pressure and the forward flow of the blood, which is known as the the chest pump theory (6). If venous cannulation has not

Table 1. A classification method used to define the acceptability of methods/drugs (10).

Class I	Definitely helpful
Class IIa	Acceptable, probably helpful
Class IIb	Acceptable, an optional or alternative intervention
Class Indeterminate	Obscure
Class III	Not indicated, may be harmful

Table 2. Recommendations for administration of CPR drugs.

Drug	Indication	Class
Adrenaline		Indeterminate
Vasopressin	Alternative to adrenaline in VF/pulseless VT	
	refractory to three initial shocks	IIb
Amidarone	Following adrenaline as early as after the third shock provided	
	in the treatment of shock refractory VF/pulseless VT	IIb
Lidocaine	Alternative if amiodarone is unavailable	IIb
Procainamid	Alternative if amiodarone is unavailable	IIb
Magnesium	Refractory VF if suspicion of hypomagnesemia	IIb
Sodium bicarbonate	If known preexisting hyperkalemia	I
	1.If known preexisting bicarbonate-responsive acidosis	
	2.If overdose with tricyclic antidepressants	
	3. To alkalinize the urine in drug overdoses	IIa
	1.If intubated and long arrest interval	
	2.Upon return of spontaneous circulation after long arrest interval	IIb
	Respiratory acidosis	III
Calcium	Routine use	III
Atropine	Bradycardia	I?

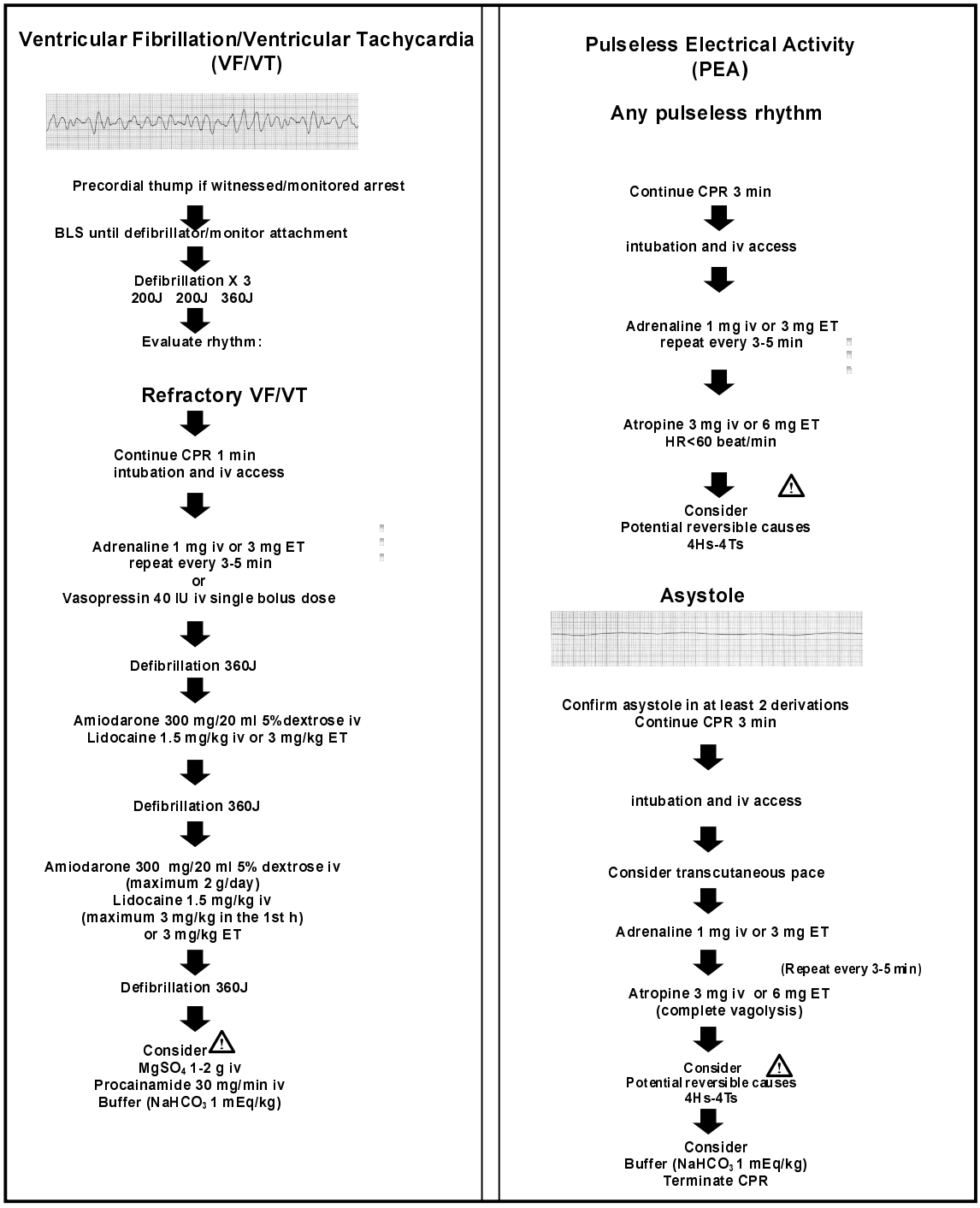

Figure. Algorhythm of advanced cardiac life support including ventricular fibrillation/ventricular tachycardia (VF/VT), refractory VF/VT, pulseless electrical activity (PEA) and asystole.

ET: Endotracheal

The 4H:
1. Hypoxia
2. Hypovolemia
3. Hyper/hypokalemia, hypocalcemia and acidemia
4. Hypothermia

The 4T:
1. Tension pneumothorax
2. Cardiac tamponade
3. Thromboembolic or mechanical obstruction (e.g.pulmonary embolism)
4. Toxic or therapeutic substances in overdose

been achieved immediately, then adrenaline 2-3 mg diluted in 10 ml normal saline (0.9%) may be administered via the endotracheal (ET) route and followed by five ventilations to aid spread throughout the lungs (6).

Since each drug used in pediatric resuscitation has a different dosage in mg/kg weight and a different presentation in ml/kg in the ampule, a common dose of 0.1 ml/kg body weight has been established in order to simplify drug use in emergency so that all the new ampules contain the same dose (8). In children, adrenaline can be given at a dose of 10 µg/kg or 0.1 ml/kg 1 in 10000 solution (1).

Dose dependent improvement in regional myocardial and cerebral blood flow has been recorded in various studies but no improvement in hospital discharge and survival has been seen (1,6). High doses up to 0.2 mg/kg adrenaline may further enhance coronary perfusion pressure, but does not seem to improve long-term survival after out of hospital or in hospital cardiac arrest (4). On the other hand a higher dose of 0.01 to 0.1 mg/kg improved the resuscitation rate from 40% to 90% (5). Comparison of standard and high doses of adrenaline did not show statistically significant improvement. In addition to the detrimental effects of beta 1 and alpha 1 actions of adrenaline, it induces disproportionate increases in systolic pressures of the pulmonary artery, pulmonary capillary, and pulmonary venous pressure. Excessive increases in pulmonary capillary filtration pressure may precipitate pulmonary edema (5).

Noradrenaline (norepinephrine)

Noradrenaline is a potent adrenergic agonist that stimulates alpha 1 and 2 receptors with a minor beta 2 receptor activity. In contrast to adrenaline it produces greater vasoconstriction such that total peripheral resistance is significantly increased. Increase in both myocardial and cerebral blood flows are comparable with that produced by adrenaline. It also acts on beta 1 receptors and thereby increases myocardial oxygen consumption and the risk of ischemic injury during CPR (5).

Alpha adrenergic agonist

Activation of alpha-1 adrenergic receptors result in increased peripheral vascular resistance and myocardial and cerebral perfusion pressure as well as blood flows. Predominant alpha-1 agonists such as phenylephrine and methoxamine, specifically increase peripheral vascular resistance (5). However, alpha-1 adrenergic is rapidly desentisized in the ischemic myocardium. Stimulation of myocardial alpha-1 receptors increases both inotropic and chronotropic responses leading to increase in myocardial oxygen consumption and this augments global ischemic injury (5).

Alpha-2 adrenergic agonist

Stimulation of postsynaptic alpha-2 adrenergic receptors increases endothelial nitric oxide production which counterbalances coronary vasoconstriction induced by alpha-2 adrenergic stimulation. Stimulation of presynaptic alpha-2 adrenergic receptors inhibits the release of endogenous catecholamine, which is beneficial because of the greater levels of endogenous catecholamines during CPR (5). There are three subtypes of alpha-2 receptors. Central vasodilator effects are mediated by 2A and 2C, peripheral vasoconstrictor effects are mediated by 2B(5).

It has beeen reported that a selective alpha-2 adrenergic agonist alpha-methyl norepinephrine without central negative inotropic and chronotropic effects is as effective in restorating spontaneous circulation after untreated VF for CPR and demonstrates less postresuscitation myocardial injury in animal studies (9).

Nonadrenergic vasopressors

Vasopressin

Vasopressin has been shown to significantly raise coronary perfusion pressures and to increase the return of the rate of spontaneous circulation (6). It acts on non-adrenergic V1 receptors and has been recommended in case of fibrillatory arrest as 40 IU as an iv single dose (Figure). It has several advantages over adrenaline in CPR due to lack of the beta effect and impact of acidosis on its efficacy, and lower incidence of post resuscitation myocardial dysfunction (1).

Endogenous arginine vasopressin is called antidiuretic hormone (ADH) and is released from the posterior pituitary in response to increased serum osmolality or reduced plasma volume. Under normal conditions it regulates water balance without producing hypertension

despite its high circulating levels. On the other hand in shock states, its vasopressor action is greatly enhanced. Vasopressin acts via specific renal (V-2), and vascular (V-1) receptors. It produces vasoconstriction in non vital circulations like skin, skeletal muscle, and small bowel, thereby diverting the blood to the brain, heart, and kidneys. The vasopressin analogue desmopressin is mainly a V-2 agonist but has 0.4% of the pressor activity of arginine vasopressin. Plasma half life of vasopressin is 24 min and two thirds of it is metabolized by the kidneys (5).

According to the current CPR guidelines, use of vasopressin as an alternative to adrenaline for shock refractory ventricular fibrillation is recommended as a Class IIb (Table 1, 2) (10). Use of vasopressin in patients with asystole or pulseless electrical activity (PEA) or in infants and children is recommended as Class indeterminate (5). It is not established whether a second dose of vasopressin is required or not (1).

Since vasopressin is one of the most important endogenously released stress hormones during shock, vasopressin and its analogs may also be useful to treat septic and catecholamine-resistant shock and reduce bleeding and mortality associated with esophageal variceal hemorrhage (11,12).

It has been reported that vasopressin and adrenaline were equally effective in CPR in the rat asphyxia model in the short period (13). In addition to this study, it has been shown that the triple drug therapy combination of adrenaline, vasopressin and nitroglycerine significantly improved both left ventricular, and cerebral perfusion during CPR compared with adrenaline alone (14). In another study repeated administration of combination of vasopressin and adrenaline ensured long term survival with full neurologic recovery in the prolonged CPR model of pigs (15). It has been reported that spontaneous circulation immediately returned following a single dose (40 IU) of vasopressin in refractory cardiocirculatory arrest to 2 mg iv adrenaline in a 19 year old female with prolonged hypothermia after near drowning (16). This case report showed that vasopressin could be beneficial in restoring spontaneous circulation even during hypothermic CPR prior to rewarming, in contrast to the CPR guidelines of European Resuscitation Council not to administer vasopressors to support coronary perfusion pressure during hypothermic CPR (17).

Angiotensine II (AT-II)

Angiotensin II is approximately 40 times more potent than norepinephrine It increases peripheral vascular resistance via direct and indirect vasoconstrictor effects on precapillary arterioles and postcapillary venules. Vasoconstriction is induced by activation of AT-1 receptors on vascular smooth muscle cells. AT-II causes release of endogenous catecholamines from the adrenal medulla leads to peripheral vasoconstriction. Intravenous injection of angiotensin II during CPR further increases already increased serum concentrations of endogenous adrenaline and noradrenaline (5).

Endothelin-1

Endothelin-1 carries potent nonadrenergically mediated vasoconstrictor properties by increasing calcium concentration within vascular smooth muscle cells via a nonadrenergic pathway. It is hemodynamically more advantageous than adrenaline because of lacking beta adrenergic effects. The peripheral effects of endothelin improve coronary perfusion pressure and cerebral blood flow. Endothelin-1 levels are either normal or elevated in human survivors of cardiac arrest during CPR. Long half life of endothelin could result in a worsened postresuscitation outcome. Therefore, the vasoconstrictor effect of endothelin-1 should be further investigated in setting of cardiac arrest (5).

Antiarrythmic agents

The use of antiarrythmic drugs has been recommended to aid electrical defibrillation, to prevent the reoccurrence of ventricular fibrillation and to terminate serious electrical arrythmias (6). Antiarrythmic drugs should increase the likelihood of successful defibrillation by suppressing a variety of potentially malignant arrhythmias (5).

Amiodarone

Amiodarone should be considered as a Class IIb, following adrenaline, to treat shock refractory VF/VT as early as after three shocks are provided (3). Amiodarone improves survival to hospital admission but not to hospital discharge because of the side effects such as hypotension and bradycardia (5).

Amiodarone does prevent ventricular arrhythmias and animal studies demonstrated that it could reduce the defibrillation threshold (6). In an experimental model of persistant VF, animals receiving amiodarone alone had significantly lower resuscitation generated aortic (systolic and diastolic), right atrial systolic and coronary perfusion pressures than did either adrenaline alone or the combination of amiodarone and adrenaline. This study suggested that for optimal hemodynamic support during ongoing CPR adrenaline or other vasoconstrictive agents should be given in combination with, or precede, the administration of amiodarone (18).

Amiodarone has many different hemodynamic effects. It blocks potassium channels leading to prolongation in the duration of the action potential. It also causes block in sodium and calcium channels and alpha and beta adrenergic receptors. As a result of its direct effect on smooth muscle, and its ability to block calcium channels and alpha adrenergic receptors, amiodarone dilates coronary arteries. It also dilates peripheral arteries leading to vasodilatation and reduction in afterload and systemic blood pressure. Hypotension complicates its use particularly in the setting of a rapid infusion. Therefore, amiodarone is effective in treating most ventricular and supraventricular tachyarrythmias (5).

The recommended dose of amiodarone is 300 mg diluted in 20 ml 5% dextrose as an iv bolus via a peripheral vein when there is no central venous route (3). It should be given after the third shock without allowing delay in the delivery of the fourth shock (5). A further dose of 150 mg amiodarone may be required in refractory cases followed by an infusion of 1 mg min^{-1} for 6 h and then 0.5 mg/min to a maximum of 2 g in 24 h. However, according to European datasheet maximum dose of amiodarone is 1.2 g in 24 h (3).

It has been reported that dogs receiving amiodarone alone had significantly lower resuscitation generated aortic systolic and diastolic and right atrial systolic and coronary perfusion pressures than did either adrenaline alone or the combination of amiodarone and adrenaline in the persistent VF model (18).

Lidocaine

Lidocaine is a second choice after amiodarone and procainamid. It is acceptable for use in pVT after defibrillation, hemodynamically unstable ventricular premature contractions and hemodynamically stable VT (1). Its clinical efficacy in refractory VF led to an indeterminate Class (4). It has been used to treat resistant VF if amidoarone is not available (3). However, studies have shown that lidocaine offers no improvement in survival from VF. It may actually raise the defibrillation threshold and prevent the recurrence of VF after successful defibrillation (6).

The recommended dose is 1-1.5 mg/kg iv bolus and is repeated in the dose of 0.5-0.75 mg/kg not exceeding 3 mg/kg/h. Continuous infusion of 1-4 mg/min is started only if spontaneous circulation returns during CPR (1).

Procainamide

It is an other alternative to amiodarone but the necessity for relatively slow rate of infusion (30 mg min^{-1} to a total of 17 mg/kg) makes it a less favorable option (3).

Magnesium

The antiarrhythmic action of magnesium is mediated by the activation of membrane sodium-potassium adenosine triphosphatase and blocking of slow calcium channels (4). Magnesium is universally accepted for the therapy of torsades de pointes (15). 1-2 g (4-8 mmol) of magnesium sulphate diluted in 100 ml of 5% dextrose is recommended to be given over 30-60 min followed by an infusion of 0.5 -1 g/h (1). Its use is recommended for shock refractory VF when hypomagnesemia is suspected e.g patients on potassium losing diuretics, because magnesium mirrors the action of extracellular potassium in stabilizing myocardial cell membrane (1,3,4).

Others

Atropine

Atropine enhances automacticity and conduction of both sinoatrial and atriventricular node. It is most effective in hemodynamically significant bradycardia due to vagal stimulation (1). The recommended dose in PEA associated with bradycardia (<60 beat/min) and asystole is 3 mg iv and 6 mg ET (1, 3). For the treatment of sinus bradycardia, 0.5 mg (approximately 10 μg kg^{-1}) iv should be given and repeated if required up to a total dose of 40 μg kg^{-1} (1).

Calcium

Despite the fact that extracellular calcium enhances the contractile force of cardiac muscle, there is no evidence to indicate that calcium administration during CPR improves cardiac performance. In fact ischemia promotes intracellular calcium accumulation, leading to membrane disruption and uncoupling of oxidative phosphorylation (10). Because of the risk of calcium accumulation and subsequent cell injury during periods of tissue ischemia, it is indicated when the patient exhibits acute calcium channel blocker toxicity or if there is evidence of ionized hypocalcemia or hyperkalemia. The recommended dose of calcium gluconate is 0.5 ml kg^{-1} (maximum 20 ml) of a 10% solution of calcium chloride in a dose of 0.2 ml kg^{-1} (maximum 10 ml) (1).

Sodium bicarbonate ($NaHCO_3$)

Bicarbonate therapy should be considered only after the confirmed interventions such as defibrillation, cardiac compression, intubation, ventilation and vasopressor therapy have been ineffective (1). The recommended bicarbonate administration is shown in Table 2. The bicarbonate therapy should be guided by determining the bicarbonate concentration or calculating the base deficit obtained from arterial blood gas analysis (1).

Conclusion

Survival following cardiac arrest mostly depends on the interval between collapse to initiation of CPR and collapse to defibrillation. Although no drug has been reliably proven to increase survival to hospital discharge after cardiac arrest, basic cardiac medication drugs used during ACLS were reviewed. For example; vasopressin has been recommended in case of fibrillatory arrest, the use of lidocaine in refractory ventricular fibrillation remains contentious, whereas amiodarone is recommended after defibrillation and adrenaline. Lidocaine and procainamide are alternatives if amiodarone is not available. Amiodarone may improve short term survival after out-of-hospital ventricular fibrillation cardiac arrest. Magnesium therapy is recommended especially for torsades de pointes and shock resistant ventricular fibrillation associated with hypomagnesemia. Atropine is the drug of choice in PEA associated with bradycardia and asystole. Sodium bicarbonate and calcium indications are restricted. It is still difficult to say whether drugs used during ACLS are really effective unless further prospective randomized human studies are completed.

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