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Review

The role of Levosimendan in cardiopulmonary resuscitation

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ABSTRACT

Although initial resuscitation from cardiac arrest (CA) has increased over the past years, long term survival rates remain dismal. Epinephrine is the vasopressor of choice in the treatment of CA. However, its efficacy has been questioned, as it has no apparent benefits for long-term survival or favorable neurologic outcome. Levosimendan is an inodilator with cardioprotective and neuroprotective effects. Several studies suggest that it is associated with increased rates of return of spontaneous circulation as well as improved post-resuscitation myocardial function and neurological outcome. The purpose of this article is to review the properties of Levosimendan during cardiopulmonary resuscitation (CPR) and also to summarize existing evidence regarding the use of Levosimendan in the treatment of CA.

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Contents

1. Introduction	596
2. Levosimendan's actions	597
3. Effects of Levosimendan during cardiopulmonary resuscitation	597
4. Levosimendan in post-cardiac arrest myocardial dysfunction	599
5. Levosimendan in post-cardiac arrest brain injury	600
6. Conclusion	600
Acknowledgments	600
References	600

1. Introduction

Although the rates of initial resuscitation from cardiac arrest (CA) have increased over the past years, long term survival rates remain dismal (Berdowski et al., 2010). Epinephrine is the vasopressor of choice in the treatment of CA because it increases coronary perfusion pressure (CPP) and thus return of spontaneous circulation (ROSC) (Callaway, 2013). However, the efficacy of epinephrine in the setting of CA has been questioned because it has no apparent benefits for long-term survival or neurologic

outcome (Xanthos et al., 2011). Moreover, modern management of CA should aim at improving not only ROSC rates but also long-term survival.

Levosimendan is a unique inodilator (Endoh, 2001), with cardioprotective and neuroprotective effects (Niemenen et al., 2013). Levosimendan is the treatment of choice in acute and decompensated chronic heart failure states (Berger et al., 2007). Moreover, Levosimendan may be particularly beneficial in the treatment of post-operative myocardial dysfunction following cardiac surgery (De Hert et al., 2007), right ventricular failure (Poelzl et al., 2008) and sepsis (Zager et al., 2006). Several studies suggest that the administration of Levosimendan during cardiopulmonary resuscitation (CPR) and the post-resuscitation phase is associated with increased rates of ROSC (Koudouna et al., 2007), as well as improved post-resuscitation myocardial function (Huang et al., 2005a) and

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neurological outcome (Kelm et al., 2014). Although the use of Levosimendan has not been implemented in the latest guidelines on resuscitation (Nolan et al., 2010), its pharmacological actions make it a promising agent in the treatment of CPR.

The purpose of this article is to review the properties of Levosimendan during CPR and also to summarize existing evidence regarding its use in the management of CA.

2. Levosimendan's actions

Levosimendan is a non-adrenergic inotropic calcium sensitizer (Endoh, 2001) that exerts its inotropic effect principally via binding to the Ca^{2+} saturated troponin C of the myocardial thin filament (Jamali et al., 1997). Its ability to enhance calcium responsiveness of the myofilaments potentiates cross-bridge formation, thereby augmenting contractility and enhancing relaxation (Haikala et al., 1995; Janssen et al., 2000). Moreover, it has anti-stunning effects and reduces post-resuscitation myocardial dysfunction (Figgitt et al., 2001).

Levosimendan has also vasodilatory and anti-ischemic effects mediated by the opening of ATP-sensitive potassium (K_{ATP}) channels in the sarcolemmal membrane of vascular smooth muscle cells (Kaheinen et al., 2001). It induces vasodilation in systemic circulation (De Witt et al., 2002; Slawsky et al., 2000) and lowers both preload and afterload, improving tissue perfusion. It also exerts some vasodilator effects on the coronary (Michaels et al., 2005) and cerebral circulation (Kelm et al., 2014). By the opening of mitochondrial K_{ATP} channels in cardiomyocytes, it exerts pleiotropic effects and appears to be improving long-term benefit in CA (Nieminen et al., 2013). Levosimendan has pre-conditioning and anti-apoptotic properties (Kersten et al., 2000), which protect mitochondria from ischemia–reperfusion (I/R) injury. Moreover, it exerts some anti-inflammatory effects (Parissis et al., 2004) (Fig. 1).

However, the use of Levosimendan may as well have adverse effects. Its use has been associated with both hypotension and hypokalemia (Mebazaa et al., 2007), and its use has been associated with increased frequency of both atrial fibrillation and

ventricular tachycardia (Moiseyev et al., 2002). It is known that Levosimendan has the ability to inhibit phosphodiesterase III and open K_{ATP} channels, which might provoke arrhythmogenesis (Gruhn et al., 1998). Inhibition of phosphodiesterase III increases calcium entry into the myocardial cell and enhances atrioventricular conduction (Arnold, 1993). Moreover, the activation of K_{ATP} channels during myocardial ischemia increases potassium efflux and may lead to action potential shortening and depolarization of the resting membrane. The above electrophysiological changes may facilitate the development of tachyarrhythmias (Hatcher et al., 2011).

3. Effects of Levosimendan during cardiopulmonary resuscitation

CPP, defined as the difference between the aortic pressure and the pressure in the right atrium at the onset of diastole (Paradis et al., 1990), is known to be a prognostic factor for ROSC and survival in the setting of CPR (Frenneaux, 2003). Although epinephrine induces vasoconstriction and increases CPP (Xanthos et al., 2011), it exposes the myocardium to a vigorous increase in oxygen demand through its beta adrenergic effect. Epinephrine triggers calcium influx into the myocytes by increasing intracellular cAMP levels. The increased cytosolic Ca^{2+} increases myocardial oxygen consumption (Ornato, 1993; Slawsky et al., 2000) and results in critically decreased endocardial blood flow as well as in ischemic injury.

In contrast to classic inotropic agents, Levosimendan elevates the oxygen availability to the myocardium during CPR, reducing the pressure of the right atrium due to its peripheral vasodilatory effect (Tavares et al., 2008), which leads to higher CPP. The blood supply to the myocardium is therefore enhanced at a time when oxygen requirements are increased (Gregorini et al., 1999). The enhanced myocardial contractility produced by Levosimendan (Endoh, 2002) along with the higher CPP allows the maintenance of an adequate cardiac output during resuscitation. Furthermore, Levosimendan has a direct vasodilator effect on coronary arteries (Gruhn et al., 1998) and enhances coronary blood flow (Kivikko and Lehtonen, 2005). In this way it counteracts intramyocardial coronary arteriolar vasoconstriction induced by the alpha-1 adrenergic action of epinephrine. Koudouna et al. conducted an animal study in order to test whether the addition of Levosimendan to epinephrine would result in an increased CPP. Ventricular fibrillation was induced in 20 piglets and left untreated for 8 min. The animals were randomized to receive Levosimendan (0.012 mg/kg) or placebo combined with epinephrine (0.02 mg/kg) at the beginning of CPR. The CPP was significantly higher during CPR in the group of animals that received Levosimendan and epinephrine ($P < 0.05$). Furthermore, initial resuscitation success was improved when epinephrine was combined with Levosimendan instead of placebo in the pigs (Koudouna et al., 2007) (Table 1).

Prolonged CA is accompanied with global hypoxia and severe acidosis that depresses myocardial function by impairing the responsiveness of myofilaments to Ca^{2+} (Than et al., 1994; Wayne et al., 2002). Although catecholamines remain the mainstay of treatment in the setting of prolonged CA, studies have shown that acidosis limits their effectiveness to reverse acidosis-induced myocardial contractile impairment (Hindman, 1990; Wayne et al., 2002). Prolonged CA leads to beta-adrenergic receptor down-regulation (Modest and Butterworth, 1995), reduction of formation of cAMP (Tanaka et al., 1998) and inhibition of Ca^{2+} exchange. Catecholamine resistant CA lead to the false need for multiple repetitive doses of epinephrine (Achleitner et al., 2000; Wenzel et al., 1999), which is an independent predictor of poor neurologic outcome (Behringer et al., 1998).

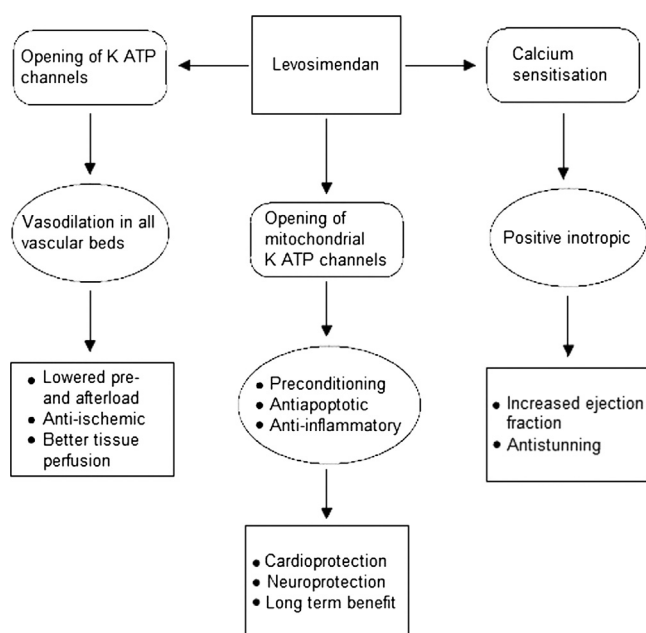


Fig. 1. Beneficial effects of levosimendan during cardiopulmonary resuscitation.

Table 1
Animal studies regarding the use of Levosimendan in models of cardiac arrest.

Study	Material	Outcomes
Koudouna et al. (2007)	Epinephrine and epinephrine + Levosimendan (0.012 mg/kg) were given in each group of 10 pigs while in ventricular fibrillation	Combined epinephrine and Levosimendan significantly improved CPP and initial resuscitation success compared to epinephrine
Huang et al. (2005a)	15 Rats were subjected to 8 min of untreated CA. Levosimendan (bolus 12 µg/kg over 10 min and infusion 0.3 µg/kg/min for 230 min), dobutamine, or saline as placebo were given in each group 10 min after ROSC	Levosimendan improved postresuscitation myocardial function and increased the duration of survival compared with dobutamine and saline as placebo
Huang et al., 2005b	15 Pigs were subjected to 7 min of untreated CA. Levosimendan (bolus 20 µg/kg over 10 min and infusion 0.4 µg/kg/min for 220 min), dobutamine or saline as placebo were given in each group 10 min after ROSC	Levosimendan produced significantly greater left ventricular ejection fraction and fractional area changes compared with dobutamine and placebo
Wang et al. (2005)	15 Pigs were subjected to 7 min of untreated CA. One group of animals received while in CA. The other group received propranolol while in CA and levosimendan (bolus 20 µg/kg and infusion 0.4 g/kg/min for 220 min) 10 min after ROSC. The third group received saline during CA and 10 min after ROSC	Initial treatment with propranolol during CPR followed by levosimendan, after ROSC led to significant improvement in myocardial contractile function compared to the other groups
Xanthos et al. (2009)	Epinephrine, epinephrine + atenolol, epinephrine + Levosimendan (0.012 mg/kg) and epinephrine + atenolol + Levosimendan (0.012 mg/kg) were given in each group of 15 pigs while in ventricular fibrillation	Epinephrine combined with administration of atenolol and levosimendan resulted in improved postresuscitation cardiac function and 48-hour survival.
Cammarata et al. (2006)	15 Rats were subjected to 6 min of untreated CA. One group received glibenclamide 45 min before CA and levosimendan (2.5 mg/ml) during CA. The other two groups received levosimendan or saline as placebo while in CA	Levosimendan resulted in improved postresuscitation myocardial function and survival compared with placebo
Kelm et al. (2014)	43 Animals were subjected to asphyxial CA. 22 animals received levosimendan (bolus 12 µg/kg and infusion for 3 h [0.3 µg/min/kg]) and 21 animals received vehicle using saline bolus during CPR and infusion for 3 h	Levosimendan administration during CPR resulted in increased cerebral blood flow and improved neurological outcome compared with placebo

CA Cardiac arrest; CPP Coronary perfusion pressure; ROSC Return of spontaneous circulation; CPR cardiopulmonary resuscitation.

Table 2
Case reports regarding the use of levosimendan in clinical cardiac arrest.

Study	Population	Outcomes
Tsagalou and Nanas (2006)	Case report	One patient
Carev et al. (2013)	Case series	Four patients
Krumnikl et al. (2006)	Case report	One patient

Administration of Levosimendan infusion (0.3 µg/kg/min) restored spontaneous circulation, after lengthy CPR in a patient with idiopathic cardiomyopathy

Administration of Levosimendan during perioperative refractory CA, after conventional treatment with standard CPR had failed, improved myocardial function

The addition of Levosimendan in a bolus dose of 12 µg/kg and subsequent continuous infusion of 0.2 µg/kg/min following ROSC in a patient suffering from a catecholamine resistant CA, resulted in hemodynamic stabilization within 30 min after ROSC.

CA Cardiac arrest; CPR cardiopulmonary resuscitation; ROSC Return of spontaneous circulation.

Although Levosimendan is often applied as a “last resort” therapy during CPR, its beneficial effects make it an attractive agent in the setting of prolonged CA. Levosimendan actually has the potential to preserve myocardial contractile function during prolonged acidotic CA because of its unique myofilament action (Schwarte et al., 2011). Several case reports have shown that Levosimendan represents so far a final option after failure of standard treatment in refractory CA. Tsagalou and Nanas (2006) reported a case of a young man with severe congestive heart failure due to idiopathic cardiomyopathy, who developed ventricular tachycardia followed by pulseless electrical activity. Haemodynamics could not be restored after a prolonged resuscitation effort with high doses of epinephrine, norepinephrine and dobutamine. The administration of Levosimendan infusion (0.3 µg/kg/min) restored spontaneous circulation after lengthy advanced cardiac life support attempts (Tsagalou and Nanas, 2006). Moreover, Carev et al. described a case series of 4 patients with myocardial dysfunction with low ejection fraction undergoing cardiac surgery. Levosimendan was administered to them during peri-operative refractory CA after conventional treatment with standard CPR had failed. Although this case series was too small and too heterogeneous to draw safe conclusions, it appears that Levosimendan improved myocardial function in the otherwise compromised myocardium in the peri-operative setting. The authors suggest that in low output states following cardiac surgery, Levosimendan may provide inotropic support after the failure of current protocols and may have an added cardioprotective benefit, reducing further myocardial damage (Carev et al.,

2013) (Table 2). Large scale, randomized controlled clinical trials must be undertaken in order to further address Levosimendan's efficacy in CA.

The addition of Levosimendan during CPR may as well increase the potency of catecholamines. Levosimendan exerts its action without activation of adrenergic receptors, with an additive effect to the classical inotropic support (Toller et al., 2005). Moreover, with Levosimendan's administration the dose of catecholamines may be reduced, which decreases myocardial oxygen demand and preserves hemodynamic stability (De Hert et al., 2007). In a case report, a patient suffering from post-partum atonic uterine bleeding had a catecholamine resistant CA. ROSC was achieved after more than 90 min of CPR with hemodynamic instability. The addition of Levosimendan in a bolus dose of 12 µg/kg and subsequent continuous infusion of 0.2 µg/kg/min following ROSC resulted in hemodynamic stabilization within 30 min. The beneficial effects of Levosimendan in this patient suggest an important role of levosimendan for CA refractory to the usual therapeutic regimen (Krumnikl et al., 2006).

Levosimendan may be particularly effective in a clinical setting of coronary artery disease and pre-existing left ventricular dysfunction in the CA setting. The compromised myocardium is associated with significant increases in sympathetic activity which lead to a compromised oxygen balance. Energy-consuming, adrenergic effects in the otherwise compromised myocardium of CA patients might worsen myocardial ischemia (Carev et al., 2013; Huang et al., 2005b). Levosimendan does not increase myocardial oxygen consumption, since this is detrimental in the setting of a

hyper-adrenergic state of a compromised myocardium during resuscitation. In addition, it improves myocardial bioenergetics, which is beneficial for a compromised myocardium (Huang et al., 2005b).

4. Levosimendan in post-cardiac arrest myocardial dysfunction

Post-resuscitation myocardial dysfunction contributes to the poor long-term outcomes and includes myocardial stunning, arrhythmias and cardiomyocyte death (Chalkias and Xanthos, 2012a). Myocardial stunning is characterized by a reversible combined systolic and diastolic left ventricular contractile dysfunction, which follows a period of non-lethal ischemia despite the restoration of normal blood flow (Tang et al., 1995, 1993; Kern et al., 1996). Free oxygen radicals and abnormal calcium homeostasis are important factors for the development of myocardial stunning (Bollí and Marbán, 1999). In the immediate post-resuscitation phase there is a massive burst of reactive oxygen species generation (Tang et al., 1993), which suppresses ATP production (Goldhaber and Qayyum, 2000). The low levels of ATP and the increased amounts of reactive oxygen species impair the function of ion pumps and preserve the intracellular Ca^{+2} influx, leading to calcium overload. Furthermore, myocardial cell membranes are disrupted, with consequent cytosolic calcium overload. In myocardial stunning the cytosolic calcium overload impairs contractile function by decreasing the calcium sensitivity of the contractile proteins (Moens et al., 2005; Opie, 1989; Schwarte et al., 2011).

β -Adrenergic inotropic agents and especially dobutamine have been recommended for the treatment of post-resuscitation myocardial dysfunction. However, their use is associated with increased energy consumption and arrhythmogenesis, due to elevated intracellular calcium concentration and it may exacerbate myocardial ischemic injury (Rooke and Feigl, 1982; Steenbergen et al., 1987). In the stunned myocardium, the contractile function is already depressed and the Ca^{2+} homeostasis is already disturbed (Wei et al., 2007), thus further increase of the Ca^{2+} concentration will likely cause cardiac arrhythmias and myocardial cell injury (Endoh, 2007). Unlike agents that act through adrenergic pathways, Levosimendan enhances myocardial contraction by improving the use of available calcium rather by inundating the cell with excessive calcium. In this way the increases in myocardial oxygen consumption are minimized and the myocardial ATP concentrations are preserved (Haikala et al., 1995).

Due to the adverse effects of conventional inotropes, studies have tested the efficacy of Levosimendan as an alternative inotropic agent for the management of post-resuscitation myocardial dysfunction. In a preliminary animal study of prolonged CA, rats were randomized to undergo treatment with Levosimendan, dobutamine or saline-solution placebo 10 min after ROSC. The authors have demonstrated that dobutamine and Levosimendan exert comparable hemodynamic actions and improve myocardial function and cardiac output compared with placebo. Levosimendan offered greater survival benefit in association with smaller increases in heart rate and more favorable filling pressures compared with dobutamine and placebo ($P < 0.05$). The inotropic and chronotropic actions of dobutamine provoked disproportionate increases in myocardial oxygen consumption and impaired the oxygen supply-demand balance (Huang et al., 2005a) (Table 1). Moreover, in comparison with dobutamine, Levosimendan preserved high energy supplies, thereby minimizing severity and progression of post-resuscitation myocardial stunning. In addition to that, Huang et al. conducted an animal study where resuscitated pigs were randomized to treatment with high dose of

Levosimendan (bolus 20 $\mu\text{g}/\text{kg}$ over 10 min and infusion 0.4 $\mu\text{g}/\text{kg}/\text{min}$ for 220 min), dobutamine (5 $\mu\text{g}/\text{kg}/\text{min}$ for 230 min) or placebo. In agreement with the previous study, Levosimendan and dobutamine produced a comparable increase in cardiac output. However, the contractile function measured by left ventricular ejection fraction and fractional area change was significantly better in the Levosimendan group than in the dobutamine and placebo groups ($P < 0.05$). Moreover, although Levosimendan has vasodilatory actions and the authors expected mean arterial pressure (MAP) to decrease, the increase in cardiac output precluded a decrease in MAP. Nevertheless, this study had limitations, as only single-dose regimens of Levosimendan were employed and the dose of Levosimendan was higher than the recommended. Thus, it remains possible for alternative doses of these drugs to be leading to different outcomes. Additional response studies have to be conducted in order to precisely establish the benefit of Levosimendan in the treatment of post-resuscitation myocardial dysfunction (Huang et al., 2005b).

β -Adrenergic blockers reduce cytosolic calcium overload in the myocardium and therefore the severity of post-resuscitation myocardial injury (Gradman and Acevedo, 2002). In order to counteract the adrenergic-induced cardiac myocyte injury, studies have tested the combination of Levosimendan with β -adrenergic blocking agents. In one of the studies ventricular fibrillation was induced and remained untreated for 7 min in 15 domestic pigs, which were randomized to receive propranolol, propranolol plus Levosimendan or saline as placebo. Propranolol was administered as a bolus dose of 0.1 mg/kg during CA. Levosimendan was administered at 10 min after successful resuscitation in a dose of 20 g/kg and followed by an infusion of 0.4 g/kg/min over the ensuing 220 min. The initial treatment with propranolol during CPR followed by Levosimendan after ROSC has been shown to lead to additional and significant improvement in myocardial contractile function, compared to the other groups ($P < 0.05$) (Wang et al., 2005). In agreement with the previous study, Xanthos et al. reported that the co-administration of epinephrine, atenolol and Levosimendan during CPR in a pig model of CA minimized the severity of post-resuscitation myocardial function and resulted in improved 48-hour survival compared to the administration of epinephrine with atenolol and epinephrine with Levosimendan ($P < 0.05$). The maintenance of favorable effects of Levosimendan during β -blocker therapy is consistent with their mechanism of action, which is independent of the occupancy of the β -adrenergic receptors (Xanthos et al., 2009).

Levosimendan has cardioprotective effects and reduces the extent of myocardial ischemia-reperfusion injury (Kersten et al., 2000). It exerts pre-conditioning-like effects in the myocardium by opening of mitochondrial K_{ATP} channels in cardiomyocytes (Pollesello and Papp, 2007). Pre-conditioning is a phenomenon in which one or several brief periods of ischemia or anoxia or the administration of certain pharmacological agents initiates mechanisms which lead to the protection against subsequent, prolonged periods of ischemia or other lethal stresses. Pre-conditioning may be manifested as a marked reduction in infarct size, an amelioration of myocardial stunning or a reduced incidence of cardiac arrhythmias (Pathak et al., 2013; Tang et al., 2000). Several studies have shown that Levosimendan induces pre-conditioning and improves recovery of cardiac function after global I/R injury (Leprán et al., 2006; Öztürk et al., 2010). In a rat CA model, the administration of Levosimendan resulted in improved post-resuscitation myocardial function and survival compared with placebo ($P < 0.05$). Levosimendan minimized the severity of myocardial ischemic injury as indicated by fewer electrical shocks and lower ST-elevations. The beneficial effect of Levosimendan in improving post-resuscitation myocardial function was abolished by prophylactic administration of the non-selective K_{ATP} channel inhibitor, glibenclamide (Cammarata et al., 2006).

5. Levosimendan in post-cardiac arrest brain injury

Post-CA brain injury is characterized by the impairment of cerebral microcirculation which compromises blood flow and contributes greatly to the overall mortality (Chalkias and Xanthos, 2012b). In the early post-resuscitation period low flow states may aggravate microvascular disorders such as increased blood viscosity, platelet aggregation and leukocyte adhesion. Moreover, cerebral auto-regulation and blood brain barrier permeability is impaired, which leads to cerebral edema (Liachenko et al., 2001). Cerebral blood flow is further compromised by the dysfunction of the endothelium. Nitric oxide formation decreases, leading to impaired vasodilation and increased cerebral microvessel vascular tone (Armstead et al., 2012). Furthermore the vasoconstrictive effect of epinephrine on microvessels decreases cerebral capillary blood flow and prolongs ischemia in cerebral tissue beds (Fries et al., 2006).

K_{ATP} channels, which are present in both large cerebral arteries and microvessels, regulate cerebrovascular tone and mediate cerebrovasodilation (Toyoda et al., 1997). Levosimendan activates K_{ATP} channels and causes vasodilatation of the cerebral microcirculation, thus increasing blood flow to the under perfused cerebral parenchyma (Armstead et al., 2011). Moreover, Levosimendan through K_{ATP} channels maintains intact cerebral auto-regulation and protects from ischemia reperfusion injury (Munakata et al., 2010). It reduces non-homogeneous conditions, which are suspected to cause secondary reperfusion injuries by balancing and optimizing the vascular tone of cerebral vessels. Furthermore, the activation of K_{ATP} channels reduces the permeability of the blood–brain barrier and thus decreases cerebral edema (Zhu et al., 2008).

The neurologic outcome after CA depends strongly on the recovery of cerebral blood flow after resuscitation (Chalkias and Xanthos, 2012b). Studies have shown that Levosimendan increased cerebral blood flow and led to a favorable neurological outcome. In a study by Kelm et al., 61 rats underwent asphyxial CA and were randomized to receive Levosimendan treatment (bolus 12 $\mu\text{g}/\text{kg}$ and infusion for 3 h [0.3 $\mu\text{g}/\text{min}/\text{kg}$] or vehicle (saline 0.9% bolus and infusion for 3 h). Levosimendan significantly increased local cerebral blood flow after asphyxial CA. It also improved cerebral perfusion via increased cardiac index and vasodilatation, which led to reduced neuronal injury and improved 24 h neurological outcome after CA. MAP was decreased in animals treated with Levosimendan compared to animals treated with saline 0.9% (Kelm et al., 2014). In the post-resuscitation period, increased MAP is associated with a better neurological outcome and one would expect that the reduction in MAP would lead to neurological dysfunction (Sterz et al., 1990). However, the concurrent increase in cardiac output induced by Levosimendan, enhanced tissue microcirculation and improved cerebral blood flow.

Serum astroglial protein (S-100) and neuron-specific enolase (NSE) are markers of cerebral injury and have been shown to positively correlate with the severity of brain injury in patients with CA (Schoerhuber et al., 1999). Levosimendan exerts beneficial neuroprotective effects by reducing serum biomarkers of brain ischemia. In a CA study by Xanthos et al., the group of animals which received a combination of epinephrine plus Levosimendan and epinephrine, atenolol plus Levosimendan, had significantly lower serum levels of S-100 and NSE than those measured in the groups which received epinephrine and epinephrine plus atenolol during the entire post-resuscitation period. The authors reported that statistically significant reduction was noted in both serum levels of the biomarkers of cerebral ischemia in the groups where Levosimendan was added (Xanthos et al., 2009). Moreover, brain regional oxygen saturation (rSO₂) may serve as an indicator of brain hypoxemia (Shah et al., 2000). A decrease in rSO₂ is positively correlated to brain damage

(Orihashi et al., 2004). In a study by Koudouna et al., rSO₂ was significantly higher during CPR in animals treated with epinephrine plus Levosimendan compared to animals treated with epinephrine alone. Levosimendan enhanced cerebral blood flow, which elevated rSO₂ and ameliorated brain injury (Koudouna et al., 2007). However, the findings of the above mentioned studies must be interpreted within the constraints of several potential limitations. Cardiac indices were not directly measured and it is unknown whether Levosimendan induced hemodynamic effects altered cerebral blood flow (Koudouna et al., 2007).

Apoptotic cell death after CA is the result of a cascade of events mediated by effects of free radical production, activation of pathological protease cascades and impaired calcium homeostasis (Shimizu et al., 2002). Mitochondrial calcium overload leads to mitochondrial permeability transition pore (MPTP) opening. The MPTP, a non-specific pore of the inner mitochondrial membrane, plays an important role in apoptotic cell death since it opens during reperfusion, leading to mitochondrial damage and release of cytochrome C (Shimizu et al., 2002). Moreover, the activation of mitochondrial K_{ATP} channel plays a role in the production of cytoprotective proteins such as antioxidant enzymes and antiapoptotic proteins (Cengiz et al., 2010; Liu et al., 2002; Xing et al., 2008). Studies in I/R models have shown that the activation of the mitochondrial K_{ATP} channel may attenuate calcium overload. This reduction of mitochondrial calcium uptake would prevent, during reperfusion, the opening of the MPTP and therefore ameliorate mitochondrial damage (Bernardi and Rasola, 2007; Wu et al., 2006).

Levosimendan has also anti-inflammatory effects and may decrease the expression of pro-inflammatory mediators, indicating a diminished progression of injury (Charalampopoulos and Nikolaou, 2011). In a study of I/R injury, Levosimendan reduced brain swelling and the inflammatory response 24 h after reperfusion and the expression of TNF α (Hein et al., 2013). Moreover, in another study Levosimendan reduced inflammatory response in the spinal cord and improved function after transient ischemia (Katircioglu et al., 2008). However, in a study of asphyxial CA, Levosimendan failed to reduce inflammation in brain probably due to low brain tissue concentration (Kelm et al., 2014). Further studies must be conducted in order to determine the role of Levosimendan in the reduction of the inflammatory response after CA.

6. Conclusion

Several case reports and experimental studies suggest that Levosimendan might be of clinical benefit during CPR. Levosimendan not only increases initial resuscitation success but also exerts cardioprotective and neuroprotective effects. However, clinical data regarding the use of Levosimendan as a pleiotropic agent during CPR are scarce and restricted to single case reports. Large randomized trials must be conducted to better assess the clinical efficacy and the appropriate dosage of Levosimendan in the setting of CPR and post-resuscitation care. In addition, high quality studies focusing on morbidity and mortality outcomes are necessary, especially when repeated doses of Levosimendan are used.

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