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REVIEW

Levosimendan in acute heart failure

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ABSTRACT

Numerous adverse effects and an increased mortality are the reasons why many clinicians are often unsuccessful with the inotropic agents presently in use. New therapeutic agents have been developed in the last few years to assist the clinician in the stabilization, support and treatment of cardiovascular disease.

One of the newest groups of inotropic agents is a group of agents, which increase the affinity of myofibrils for calcium and are called calcium sensitizers. Calcium sensitizers are the newest heterogeneous group of inotropic agents. The best known representatives of this group are levosimendan and pimobendan. Positive inotropic effects of levosimendan are achieved by its binding to troponin C and calcium, thereby stabilizing the tropomyosin molecule and prolonging the duration of actin-myosin overlap without a change in the net concentration of intracellular calcium. The vasodilatory effect of levosimendan is reached through activation of ATP-dependent potassium channels. This leads to a decrease in both afterload and preload, increased coronary blood flow and a resultant anti-ischemic effect. Levosimendan is therefore categorized as an anti-ischemic inotropic agent. Furthermore, experiments have confirmed that levosimendan as an opener of KATP – channels in the mitochondria and the sarcolemma of myocites may have an effect on the myocardium preconditioning.

Key words: levosimendan, inotropic state, preconditioning, low cardiac output syndrome

In 1908, Sir James McKenzie first described "low cardiac output syndrome". Clinically, this syndrome results in global hypoperfusion, whose treatment requires inotropic support by vasoactive medications, or mechanical intervention to support and improve cardiac work. In the early 1900s' the mainstay of cardiac treatment was digitalis with the addition of a salt reduced diet. Accumulated fluids within pleural and peritoneal spaces were eliminated by mechanical means or by drainage. The use of diuretics was instituted during the 1920's. The treatment of congestive heart failure entered a second phase in the 1950's, when vasodilators were introduced into the physicians' therapeutic armamentarium. With the introduction of the inotropic agents in 1980s', a third great period in the therapy of heart failure had begun.

The catecholamine inotropic agents were among the earliest vasoactive agents and remain important and useful today although there can be some negative consequences of their use (table 1). A major side effect is an increase in myocardial oxygen consumption. (1)

A lack of tachyphylaxis and tachycardia, and being independent of β-adrenergic receptors conditions, gives a clinical advantage to phosphodiesterase III

Table 1. Adverse effects of catecholamines administration.

ADVERSE EFFECTS OF CATECHOLAMINES ADMINISTRATION
• increase of oxygen consumption
• arrhythmogenic effect
• tachyphylaxis
• increased risk of sudden cardiac death
• difficulty during β-blockers administration
• dependency about functional condition of β-adrenergic receptors

Table 2. Calcium sensitizers.

CALCIUM SENSITIZERS			
Name	**Chemical structure**	**Classification**	**Description**
EMD57033	tiadiazinone	group III	used in veterinary medicine
ORG 30029	carboximidamide	group III?	laboratory Investigation
CGP 48506	benzodiazocine	direct contact with actin (group II) or myosine??	lab. investigation
MCI-154	piridazinone	group I	clinical investigation in Japan
Pimobendan	piridazinone	group I	clinical use
Levosimendan	piridazinone	group II	clinical use

inhibitors, when comparing them with the catecholamines.

Despite having a different mechanism of action, phosphodiesterase III inhibitors, just like catecholamine inotropic agents, increase the intracellular level of calcium, thereby possibly damaging the myofibrils and causing significant rhythm disorders.

Numerous adverse effects and an increased mortality are the reasons why many clinicians are often unsuccessful with the inotropic agents presently in use. New therapeutic agents have been developed in the last few years to assist the clinician in the stabilization, support and treatment of cardiovascular disease.

One of the newest groups of inotropic agents is a group of agents, which increase the affinity of myofibrils for calcium and are called calcium sensitizers. Calcium sensitizers are the newest heterogeneous group of inotropic agents. The best known representatives of this group are levosimendan and pimobendan. Levosimendan is manufactured by the Finnish pharmaceutical company Orion and was first registered in 2000 in Sweden. The European Association of Cardiologists incorporated it into the 2005 guidelines for the treatment of acute heart failure. (2) Calcium sensitizers are divided into three groups (table 2) depending on their mode of interaction with the muscle fiber.

Positive inotropic effects of levosimendan are achieved by its binding to troponin C and calcium, thereby stabilizing the tropomyosin molecule and prolonging the duration of actin-myosin overlap without a change in the net concentration of intracellular calcium.

The vasodilatory effect of levosimendan is reached through activation of ATP-dependent potassium channels. This leads to a decrease in both afterload and preload, increased coronary blood flow and a resultant anti-ischemic effect. Levosimendan is therefore categorized as an anti-ischemic inotropic agent. (3) Additionally, the incidence

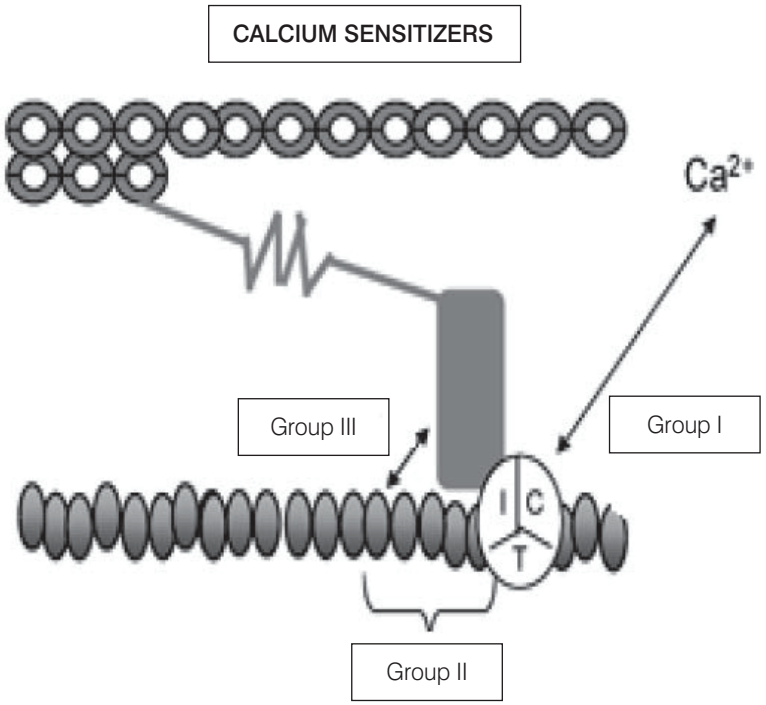

Figure 1. Mechanisms of action of calcium sensitizers.

of arrhythmias is extremely low, there is no development of tolerance to its pharmacological effects, and the simultaneous administration of β-blockers and calcium channels blockers do not produce serious adverse effects.

Clinical studies conducted on patients with acute and chronic heart failure treated with β-adrenergic agonists and phosphodiesterase III inhibitors have given evidence to the limits of their use. This is why numerous randomized clinical trials investigating the promising effects of levosimendan are being conducted. According to available data, of all the vasoactive medicaments the only vasoactive agent which improves the clinical recovery of patients with acute heart failure is levosimendan. (4)

Apart from having an acute effect, levosimendan achieves a prolonged hemodynamic effect due to its two metabolites OR-1855 and OR-1896. These two metabolites reach an optimal plasma concentration two days after being administered and they can be effective for 7-9 days after being administered via a 24 hour infusion of levosimendan.

The "Dose-ranging" study was the first double-blind and placebo controlled study analyzing the effects of different doses of levosimendan and comparing them with dobutamine and placebo. After being administered for 24 hours all doses of levosimendan statistically had a significant decrease of the PCWP in comparison to dobutamine and placebo. The infusion of different doses of levosimendan 0.4 and 0.6 μg/kg/min caused a statistically significant increase of the cardiac minute volume. (5)

The "Dose-escalation" study was conducted on 146 patients with acute heart failure and left ventricle systolic dysfunction. Levosimendan was administered as a bolus dose of 6μg/kg and subsequently as a continuous infusion up to a maximum dose of 0.4 μg/kg/min. Levosimendan had increased the stroke volume output and decreased the PCWP in comparison to placebo. With a favorable hemodynamic effect after a 6 hour administration levosimendan showed a good clinical effect significantly decreasing dyspnea and fatigue in acutely decompensate patients. (6)

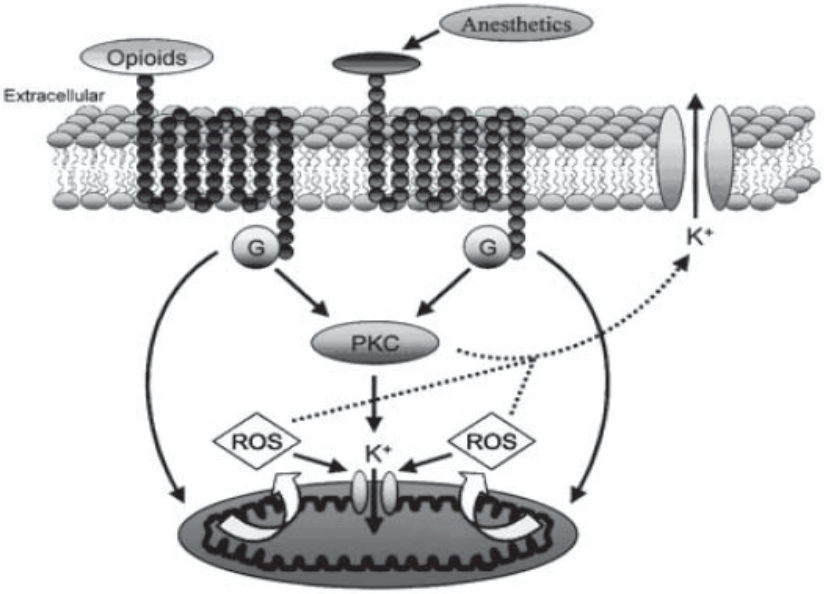

Figure 2. Preconditioning mechanisms - opening of KATP – channels in the sarcolemma and the mitochondria.

In two large randomized studies, RUSSLAN and LIDO, it was documented that positive hemodynamic effects and a lower mortality was seen in patients who received levosimendan in comparison to patients who received dobutamine or placebo. (7,8) Also, there is much interest in levosimendan administration in patients with open-heart surgery, especially in those with off-pump procedure.

Levosimendan was investigated in numerous prospective clinical studies involving patients undergoing cardiac surgery. In the first randomized and double-blind study Lileberg et al. investigated the coronary hemodynamics and oxygen consumption in the myocardium after the administration of levosimendan. Patients were divided into two groups with respect to the dose of levosimendan of 8μg/kg/min or 24μg/kg/min and placebo. After both doses of levosimendan, there was a significant rise in the cardiac minute output and a decrease in systemic and pulmonary vascular resistance. The flow through the coronary sinus increased from 28 to 42 ml meanwhile the consumption of oxygen in the myocardium remained unchanged. (9)

In a randomized placebo controlled and fourfold-blind study, the first one ever, conducted on patients who underwent OPCABG surgery, with normal left ventricle function, the authors have given evidence of new therapy options of levosimendan. Namely, the administration of levosimendan at 12μg/kg/min through 10 minutes in comparison to 24μg/kg/min and placebo showed a more favorable effect on the systolic function of the heart. In conclusion the authors recommend levosimendan as a new therapy option for the investigated group of patients. (10)

In another double-blind randomized and placebo controlled study the dose of levosimendan of 12μg/kg through 10 minutes in comparison with placebo administered to patients undergoing OPCABG surgery also had a favorable hemodynamic effect on the systolic function of the left heart. (11)

Somewhat later it was also proven that there was a prolonged favorable hemodynamic effect of levosimendan using two independent methods – thermodilution and transesophageal ultrasound. (12).

Most of our cells possess endogenous

protective mechanisms which if activated prior to ischemia protect the cell from the damage induced by ischemia. This protective mechanism is called preconditioning and the stimuli along with short-term ischemia can be some drugs. Murry et al. first described ischemic preconditioning in 1986. Warltier, two years later describes preconditioning via inhalational anesthetics. Preconditioning mechanisms are attained through the opening of KATP – channels in the sarcolemma or the mitochondria (figure 2). (13)

Experiments have confirmed the role of levosimendan as an opener of KATP – channels in the mitochondria and the sarcolemma of myocites. Tritapepe et al. (14) administered an infusion of 24μg/kg of levosimendan through 10 minutes directly prior to the application of a cardiopulmonary bypass. By monitoring the perioperative hemodynamic parameters and the concentration of cardiac troponin I through a period of 48 hours they have proven a lower postoperative concentration of troponin I ($P<0.05$) and a higher cardiac index ($P<0.05$) in comparison to the control group. The group of patients that received a short infusion of levosimendan directly prior to CABG had shown signs of less damage to the myocardium which is indicative of the effects of preconditioning.

This result is of great clinical significance because a short-term administration of levosimendan directly prior to ischemia could decrease the intraoperative damage of the myocardium.

CONCLUSION

Historically, the catecholamines inotropic agents were first line medications used in the treatment of cardiovascular compromise, but their benefits were often overshadowed by major complications, such as increased mortality. The introduction of many newer agents in newer classes, such as those which produce their effects do not change the intracellular calcium values represent safer, better choices for treatment. Furthermore, through the preconditioning mechanisms, levosimendan may have an effect on the process of perioperative protection of the myocardium.

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