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RESEARCH ARTICLE

LEVOSIMENDAN, A NEW INODILATOR AGENT REVIEW STUDY

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ABSTRACT

Levosimendan, a myofilament Ca2 sensitizer with inotropic effects, increases myocardial performance without substantial changes in oxygen consumption and with neutral effects on heart rhythm. In addition, levosimendan has vasodilatory effects that are acheived by stimulation of adenosine triphosphate–dependent potassium channels. This action may be of specific interest in the setting of myocardial ischemia.To date, levosimendan is approved in 31 countries worldwide, and more patients with heart failure have particepated in randomized controlled trials with levosimendan than with any other intravenous inotropic agent. This review compares the different actions of standard positive inotropic drugs and Ca2 sensitizers. It also summerizes the current experimental and clinical knowledge of the use of levosimendan and gives practical recommendations with a special focus on the perioperative setting.

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INTRODUCTION

Several clinical studies suggest substantial limitations of currently available positive inotropic substances, including 1-adrenoceptor agonists and phosphodiesterase III inhibitors in the short- and long-term treatment of heart failure. The reasons for these detrimental effects are related to the mechanism of action of these drugs, including increases in intracellular Ca2 with subsequent increases in myocardial oxygen demand and arrhythmogenesis. Levosimendan, a myofilament Ca2 sensitizer with inotropic effects, increases myocardial performance without substantial changes in oxygen consumption and with neutral effects on heart rhythm. In addition, levosimendan has vasodilatory effects that are achieved by stimulation of adenosine triphosphate–dependent potassium channels. This action may be of specific interest in the setting of myocardial ischemia. To date, levosimendan is approved in 31 countries worldwide, and more patients with heart failure have participated in randomized controlled trials with levosimendan than with any other intravenous inotropic agent. IN addition to administration of oxygen, diuretics, vasodilators,and anticoagulants, the support of severely impaired myocardial contractile function with positive inotropic agents represents a mainstay of therapy in critically ill patients.

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Irrespective of whether used in patients with acute decompensation of chronic heart failure (CHF), contractile dysfunction after myocardial infarction, or stunning after cardiac surgery, these drugs frequently improve contractility and relieve symptoms. Regarding clinical outcome, however, the results of many trials suggest substantial limitations of such drugs in the treatment of myocardial contractile dysfunction. With the exception of digoxin, which has neutral effects on overall mortality, currently available positive inotropic substances, including 1-adrenoceptor agonists and phosphodiesterase (PDE) III inhibitors, have been found detrimental in the long-term treatment of heart failure because they contribute to the development of malignant ventricular tachyarrhythmias and increase the incidence of sudden cardiac death. In addition, recent studies also indicate that short-term administration of PDE III inhibitors is associated with a high incidence of treatment-related complications, *e.g.*, atrial fibrillation and hypotension, particularly when concomitant ischemia is present as in patients with ischemic cardiomyopathy. The reasons for these disappointing findings may be related to the fact that, despite different primary sites of action, all of these drugs eventually enhance myocardial contractility by increasing intracellular levels of cyclic adenosine monophosphate (cAMP) in myocytes, whether generated by an increased rate of synthesis (1-adrenoceptor agonists) or by a decreased rate of degradation (PDE III inhibitors), which promotes the release of Ca2 from the sarcoplasmic reticulum (SR) to the cytosol. Augmentation of intracellular Ca2 subsequently produces a temporary improvement in contractility at the expense of an increased

myocardial energy consumption and oxygen demand, which finally accelerates myocardial cell death. Furthermore, increased concentrations of cAMP and the subsequent change in intracellular Ca2 turnover are cardiotoxic and enhance electrophysiologic mechanisms that result in rhythm disturbances. Accordingly, considerable research has been devoted to develop new approaches to positive inotropic therapy independent of the potentially deleterious mechanism of augmenting intracellular Ca2 availability. Theoretically, such approaches should enhance contractile force without increasing myocardial oxygen demand or the risk of cardiac arrhythmias. As the relation of intracellular Ca2 and corresponding tension of cardiac myofilaments may be impaired during pathophysiological conditions such as ischemia, acidosis, sepsis, or hypothermia, drugs have been developed that modulate this relation without actual alteration of intracellular Ca2 levels. All of these "myofilament Ca2 sensitizers," including levosimendan, pimobendan, EMD 57033, ORG 30029, MCI-154,and others, share the ability to enhance contractility by increasing the sensitivity of the myofilaments to calcium although with different potencies, through diverse mechanisms and sites of action, and with varying degrees of parallel PDE inhibitory effects. Among these, levosimendan is promising in the management of both acute and chronic left ventricular (LV) failure, because it is a potent Ca2 sensitizer, has no negative impact on diastolic function, has little potency for additional PDE inhibition at clinically recommended concentrations, has neutral effects on heart rhythm, and has advantages over dobutamine in long-term survival.

Levosimendan was first approved in Sweden in 2000 and is currently in clinical use in approximately 30 countries, predominately in Europe and South America. The drug is in large phase III clinical studies in the United States(REVIVE) and Europe (SURVIVE) and has been granted fast-track status by the Food and Drug Administration. The European Society of Cardiology has adopted its use in the treatment of acute heart failure in 2001 and assigned it a class of recommendation IIa (*i.e.*, conflicting evidence with weight in favor of usefulness), level of evidence B (*i.e.*, data derived from a randomized clinical trial) in the treatment of symptomatic low–cardiac output heart failure secondary to cardiac systolic dysfunction without severe hypotension in 2005, which is superior to catecholamines or PDE III inhibitors for this indication. This review compares the different actions of standard positive inotropic drugs and Ca2 sensitizers. It also summarizes the current experimental and clinical knowledge of the use of levosimendan and gives practical recommendations with a special focus on the perioperative setting.

Mechanism of Myocardial Excitation–Contraction Coupling: When the myocyte sarcolemma depolarizes, extracellular Ca2 enters the cell, primarily through sarcolemmal voltage-gated L-type Ca2 channels. This action on its own is insufficient to produce contraction of the myofilaments but triggers the (passive) release of larger amounts of Ca2 from the SR to the cytosol ("calcium induced Ca2 release"), which subsequently initiates contraction. Contraction is performed by interaction of a variety of structural and regulatory proteins, including myosin, actin, tropomyosin, and the troponin complex (TnC, TnI, TnT). When cytosolic Ca2 is low during relaxation (approximately 107M), tropomyosin inhibits interaction between actin and myosin. Contraction is initiated when cytosolic Ca2 increases (approximately105M), binds to TnC, and causes a conformational change of this protein. Subsequent activation of TnT removes tropomyosin and TnI from the adenosine triphosphate (ATP) reactive site, thus allowing actin to interact with myosin, a process known as cross-bridging. As long as Ca2 is bound to TnC, this energy-dependent process is repeatedly performed ("cross-bridge cycling")to generate contractile force. During basal states, Ca2 does not saturate the myofilaments, *i.e* approximately 25% of full activation is achieved. This reserve of activation can be mobilized by increasing either the amount of Ca2 available for binding or the sensitivity of myofilaments to Ca2. Relaxation is initiated both by phosphorylation of TnI and rapid removal of cytosolic Ca2 predominately by reuptake into the SR through the (energy requiring) sarcoplasmic endoplasmic reticulum calcium adenosine triphosphatase isoform 2 (SERCA2). With each contraction-relaxation cycle, there is no net gain or loss of cellular Ca2. Importantly, the response of myofilaments to a specific intracellular concentration of Ca2 may be attenuated (*i.e.*, "desensitization") by a variety of pathophysiologic conditions, including acidosis,hypothermia,increase dinorganic phosphate, sepsis, ischemia–reperfusion injury,and myocardial stunning, but also by pharmacologic -adrenergic stimulation or the presence of CHF with increased neurohormonal activation. Conversely, the sensitivity of contractile proteins to Ca2 may increase, *e.g.*, by -adrenergic receptor stimulation or by administration of myofilament calcium sensitizers.

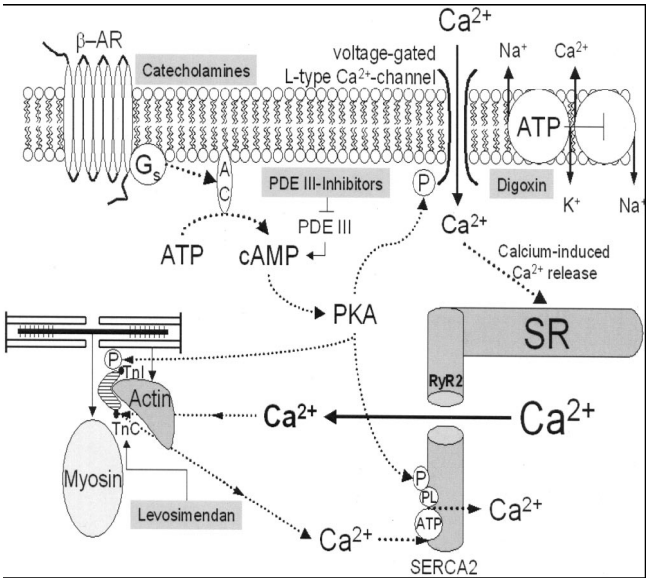


Fig. 1. Schematic illustration mechanism of action of positive inotropic drugs. -Adrenergic stimulation (catecholamines) and phosphodiesterase (PDE) III inhibition increase cyclic adenosine monophosphate (cAMP), which acts *via* protein kinaseA (PKA) to phosphorylate calcium channel protein, phospholamban (PL), and troponin I (TnI). Phosphorylation (P) ofcalcium channel protein enhances sarcolemmal inward movement of Ca2, which subsequently increases Ca2 movement from the sarcoplasmic reticulum (SR) through the calcium release channel (ryanodine receptor type 2 [RyR2]) to the cytosol(calcium-induced Ca2 release). Digoxin increases cytosolic Ca2 by inhibition of sarcolemmal Na–K–adenosine triphosphatase and Na–Ca2 exchange. Cytosolic Ca2 binds to troponin C (TnC) and initiates contraction (inotropic effect). Phosphorylation of PL enhances relaxation by increased reuptake of Ca2 back into the SR by the SR Ca2 adenosine triphosphatase isoform 2 (SERCA2) (lusitropic effect).

Phosphorylation of TnI enhances the rate of relaxation by decreasing the sensitivity of myofilaments to Ca2. Levosimendan binds to TnC during systole and thereby increases the sensitivity of myofilaments to Ca2 without alteration of Ca2 levels. AC adenylate cyclase; ATP adenosine triphosphate; -AR adrenoceptor; Gs stimulatory guanine nucleotide binding proteins.

Mechanism of action of standard inotropic drugs: Drugs currently used to achieve positive inotropic effects in the perioperative setting include catecholamines, *e.g.*, dobutamine, and PDE III inhibitors, *e.g.*, milrinone. Although these substances have different sites of action, they ultimately initiate a cascade of events that stimulate contractility by increasing intracellular Ca2 concentration (fig. 1). Binding of catecholamines to 1-adrenergic receptors on the surface of myocytes activates adenylate cyclase, which generates cAMP from ATP. cAMP activates protein kinase A, which subsequently phosphorylates (*i.e.*, attaches a phosphate group to) intracellular targets, including the voltage-gated LtypeCa2 channel, phospholamban, and TnI. Phosphorylation of sarcolemmal voltage-gated L-type Ca2 channels enhances Ca2 entry into the cytosol. The increased activity of these channels further increases "trigger calcium," leading to greater activation of the calcium release channel (RyR2) in the SR and subsequent contraction (*i.e.*, positive inotropic action of catecholamines and PDE III inhibitors). In contrast, phosphorylation of phospholamban activates SERCA2. This action increases the rate of Ca2 transport from the cytosol back into the SR during diastole and is therefore responsible for the positive lusitropic actions of catecholamines and PDE III inhibitors. Although this lusitropic action enhances relaxation, it is also crucial to ensure sufficient Ca2 availability from the SR for the next cellular depolarization and contributes to the overall gain in cardiac excitation contraction coupling that adrenergic stimulation mediates. The consequences of this increased loading of the SR with Ca2 may be a key factor in the development of Ca2-mediated arrhythmias. Phosphorylation of TnI decreases the affinity of myofilaments for Ca2 and thereby also favors relaxation. Together, these effects provide integrated response to -adrenergic stimulation that increases myocardial contractility, while in parallel supports myocardial relaxation by desensitizing myofilaments and augmenting the active removal of Ca2 from the cytosol.

Cardiac glycosides, *e.g.*, digoxin, selectively and reversibly inhibit the sarcolemmal Na–K adenosine triphosphatase in cardiac myocytes with a resultant modest increase in intracellular Na. This increase of Na subsequently inhibits extrusion of Ca2 from the cytosol into the extracellular compartment by the Na–Ca2 exchanger. Ca2 not extruded from the cytosol by this mechanism is stored in the SR and allows increased release of Ca2 during the next contraction. Digoxin is commonly not used to increase myocardial contractility in the perioperative period because of only modest positive inotropic effects and a small therapeutic range. As digoxin decreases atrioventricular nodal conduction, it is, along with amiodarone, however, useful in the control of ventricular rate during refractory atrial fibrillation.

Mechanism of action of levosimendan

Positive Inotropic Effects: Myofilament Ca2 Sensitization. Levosimendan enhances myocardial contractility by binding to the Nterminal lobe of cardiac TnC with a high affinity and stabilizing the Ca2-bound conformation of this regulatory protein. Therefore, systolic interaction of actinmyosin filaments is prolonged without alteration of the rate of cross-bridge cycling. Other myofilament Ca2 sensitizers are bound to the TnC–Ca2 complex during both systole and diastole with improvement of systolic but possible impairment of diastolic function due to facilitation of cross-bridging at diastolic Ca2 levels, whereas binding of levosimendan to TnC is dependent on the cytosolic Ca2 concentration, *i.e.*, increases during systole but is relatively unchanged during diastole,when Ca2 levels decrease. This mechanism may be the reason for the parallel enhancement of myocardial contractility and improvement of LV diastolic function without promoting arrhythmogenesis or alteration of myocardial oxygen demand in experimental and clinical studies. Phosphodiesterase III Inhibition. In addition to myofilament Ca2 sensitization, levosimendan inhibits cardiac PDE, predominately PDE III,in muscle strips from human hearts and various animal models.

This effect is observed predominately at higher concentrations (0.3 M), but is not seen (0.03 M) or is less pronounced (0.1– 0.3 M) at concentrations reflecting the clinically recommended therapeutic range of 0.03– 0.3 M (*i.e.*, 10–100 ng/ml). Therefore, at concentrations of 0.03– 0.1 M, levosimendan does not alter heart rate, cAMP levels, myocardial relaxation, and cytosolic Ca2 as assessed by aequorin light transients, although it significantly increases myocardial contractility in guinea pig hearts and shifts the graph of the relation between Ca2 and contractile force to the left. These findings indicate that levosimendan mainly acts as a Ca2 sensitizer at concentrations of 0.03– 0.1 M. Although 0.1– 0.3 M levosimendan variably alters myocardial cAMP levels, heart rate, incorporation into phospholamban, and aequorin light transients, concentrations exceeding 0.3 M consistently increase heart rate, contraction (dP/dt) and relaxation (dP/dt) as well as partial phosphorylation of phospholamban and aequorin light transients. These findings suggest a contributing role of PDE inhibition at concentrations of levosimendan exceeding 0.3 M. Important experimental and clinical differences between levosimendan and classic PDE inhibitors (*e.g.*, milrinone), however, exist. First, milrinone has no Ca2 sensitizingeffect, but in contrast decreases the sensitivity of myofilaments to Ca2 through cAMP dependent phosphorylation of TnI, whereas levosimendan has this action. Second, milrinone consistently exerts positive inotropic effects in parallel with an increase in aequorin light emission (indicating influence on Ca2 transients),whereas levosimendan at low concentrations does not have this effect despite production of positive inotropic effects, suggesting that levosimendan is more potent as a Ca2 sensitizer than as an inhibitor of PDE.

Third, metabolism of levosimendan produces a long-lasting active metabolite, OR-1896,which has similar Ca2 sensitizing properties like the parent compound but a significantly lower potential to inhibit PDE III (40-fold less potent, 3-fold less selective).Because levosimendan has a relatively short elimination half-life and the infusion is usually discontinued after 24 h, the sustained positive inotropic effects observed thereafter suggest an important role of Ca2 sensitization of this metabolite. Fourth, in clinical practice, levosimendan does not increase the incidence of arrhythmias,worsen ischemia,or negatively influence patient outcome,whereas milrinone does.

Vasodilation: Levosimendan produces vasodilation in several vasculatures including coronary, pulmonary, renal, splanchnic,

cerebral,and systemic arteries as well as saphenous, portal, and systemic veins. The underlying mechanism of vasodilation has been extensively investigated but has not yet been entirely clarified. Recent evidence proposes involvement of several systems or pathways in the vasodilating effects of levosimendan (fig. 2). An important mechanism in vascular smooth muscle of systemic, coronary, and pulmonary arteries is opening of potassium channels, including ATP-sensitive K (KATP) channels in small resistance vessels and Ca2-activated K and voltage dependent K channels in large conductance vessels.Opening of these channels hyperpolarizes the membrane, inhibits inward Ca2 current, and activates the Na–Ca2 exchanger to extrude Ca2. The resultant decrease in intracellular Ca2 produces vasorelaxation.Attenuation of levosimendan-induced dilation of coronary arteries during concomitant administration of the KATP channel antagonist glibenclamide emphasizes the role of KATP channels in this setting.

A second mechanism involved in levosimendan-induced vasdilation is reduction of Ca2 sensitivity of the (TnC-lacking) contractile proteins in vascular smooth muscle. This decrease in contractile force of vascular myofilaments occurs without a proportionate decrease in intracellular Ca2. In addition, PDE inhibition has been proposed to contribute to levosimendan-induced vasodilation because of increases in cAMP in vascular smooth muscle. This effect, however, predominately occurs at excessive doses (1 mM) of levosimendan, whereas at 3 M, vasorelaxation is different from milrinone and not affected by inhibition of protein kinase A at concentrations of 0.01–1 M. Although the importance and relative contribution of each of these mechanisms of vasorelaxation is unclear and may be different in various vessels and dependent on the dose of levosimendan, an important role of K channel opening is obvious, whereas the role of PDE inhibition remains to be defined.

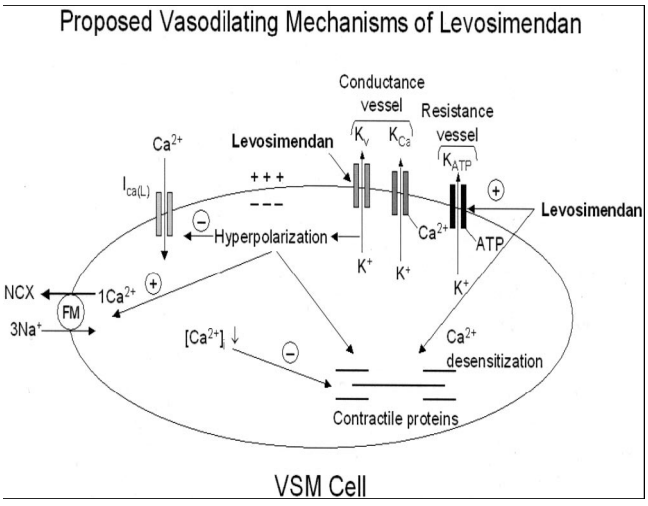
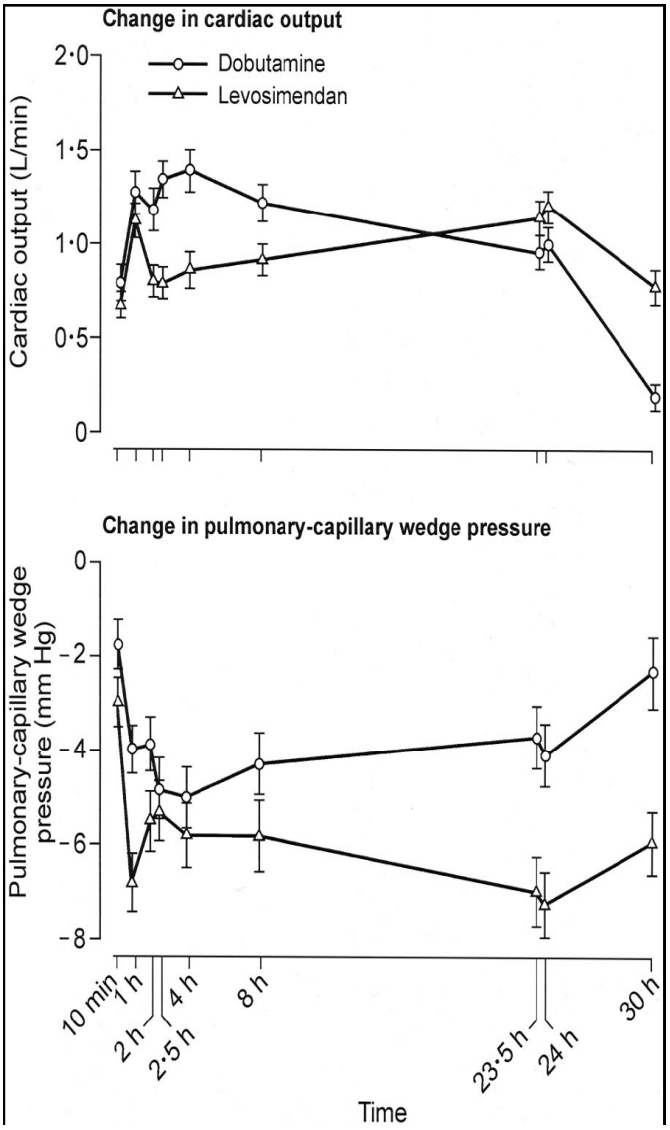


Fig. 2. Proposed vasodilating mechanisms for levosimendan. Levosimendan stimulates the adenosine triphosphate (ATP)–sensitive K (KATP) channel in small resistance vessels and the Ca2-activated K (KCa) and voltage-dependent K (KV) channels in large conductance vessels. These actions hyperpolarize the membrane, there by inhibiting inward L-type Ca2 current (ICa(L)), as well as promoting the forward mode (FM) of Na– Ca2 exchanger (NCX), *i.e.*, three Na in, one Ca2 out.
The resultant decrease in intracellular Ca2 ([Ca2]i) would produce vasorelaxation. Levosimendan also may decrease the Ca2 sensitivity of the contractile proteins directly and/or indirectly through the hyperpolarization. The *plus signs* indicate stimulation, and the *minus signs* indicate inhibition. VSM vascular smooth muscle.

***Hemodynamic Effects of Levosimendan*:** Levosimendan consistently increases cardiac output in experimental and clinical studies. Possible theoretical mechanisms of this action are modification of heart rate, improvement of cardiac performance, and vasodilation.

Heart Rate: Levosimendan dose-dependently (0.1 M) increased heart rate in several animal experiments, healthy volunteers,and patients with New York Heart Association (NYHA) functional class II–IV heart failure of ischemic etiology. The mechanism of the occasionally observed early levosimendan-induced increase in heart rate is unknown but may be produced by compensatory vasodilation-induced activation of baroreceptor reflexes, particularly after administration of a bolus. Conversely, studies demonstrate an initial neutral effect on heart rate after abandonment of a bolus, low bolus concentrations (3–12 micg/kg), or oral administration of levosimendan. In contrast, persistence of an increased heart rate after discontinuation of a 24-h infusion of levosimendan or after extended infusions for 7 days suggests an important role of OR-1896, a metabolite of levosimendan, which continues to accumulate after withdrawal of levosimendan.

In clinical practice, treatment of patients with normal or reduced ejection fraction but within the recommended dosages (6- to 24-micg/kg bolus over 10-min, followed by an infusion of 0.05– 0.2 micg/ kg/ min) rarely produces positive chronotropy exceeding more than 10% from baseline and is generally less marked in patients with severe heart failure. Accordingly, neutral or insignificant effects on heart rate were observed in patients with CHF, cardiogenic shock, and severe decompensated low-output heart failure and after myocardial infarction, but also in the perioperative period in patients undergoing surgical revascularization with normalor compromised ventricular function. In contrast, administration of high doses of levosimendan (36-micg/kg bolus and infusion of 0.3 micg/ kg/ min over 6 h) in patients with a normal ventricular function increased heart rate after cardiopulmonary bypass, particularly after the bolus (24 beats/min) and during the first hour of infusion. Therefore, changes in heart rate are obviously a function of dosage, intravascular volume status, and preexisting compromise of myocardial contractile function. Taken together, modification of heart rate under clinical conditions and within the recommended doses is unlikely to be an important mechanism of the increase in cardiac output produced by levosimendan. Fig. 3. Comparison of hemodynamic effects of levosimendan and dobutamine. Changes in cardiac output and pulmonary capillary wedge pressure were recorded from baseline to 30 h in patients with low-output heart failure. Levosimendan (0.1– 0.2 micg /kg/min) or dobutamine (5–10 micg /kg/ min) were infused for 24 h and then discontinued. At 24 h, levosimendan and dobutamine produced median changes in cardiac output of 1.09 and 0.80 l/min, respectively (*P* 0.048). In addition, administration of these drugs produced median decreases of pulmonary capillary wedge pressures of 7 and 3 mmHg, respectively (*P* 0.003). *Error bars* indicate SEMs.



Cardiac Performance: Administration of levosimendan enhances cardiac performance*in vitro*, *in vivo*, and in clinical studies. For example, in patients with low-output heart failure, a 24-h administration of levosimendan (0.1– 0.2 micg /kg/ min) increased cardiac output by 1.09 l/min and decreased pulmonary capillary wedge pressure (PCWP) by 7 mmHg, whereas dobutamine (5–10 micg /kg/ min) changed these parameters by 0.80 l/min and 3 mmHg, respectively (fig. 3). These effects generally occur in a dose-dependent manner and are characterized by an increase in LV stroke volume and cardiac index in patients with severely compromised ventricular function. In addition, improved cardiac performance has also been suggested by a significant decrease of circulating levels of amino terminal pro B-type natriuretic peptide after a 24-h infusion of levosimendan (0.1micg /kg/ min) in patients with decompensated CHF and a mean LV ejection fraction of approximately 25%. Interestingly, the decrease of this neurohormonal marker was particularly pronounced 48 h after discontinuation of levosimendan treatment.Although Ca2 sensitizers carry a potential risk of worsening diastolic function, levosimendan decreased the time constant of isovolumic relaxation in various experimental and clinical settings, indicating improvement rather than deterioration of diastolic function. In addition to these beneficial effects at rest, levosimendan treatment also improved LV systolic and diastolic performance during exercise in dogs with pacing-induced CHF.

These positive lusitropic effects may be related to the Ca2 dependence of Ca2-bound sensitization of cardiac TnC, *i.e.*, the contractile apparatus is sensitized in systole (when Ca2 is high) but not in diastole (when Ca2 is low) or alternatively due to PDEIII inhibition.

Vasodilation: Vasodilation observed with administration of levosimendan is followed by numerous consequences. Pulmonary vasodilation decreases right heart filling pressures, which, in context with positive inotropic effects, could explain increases right ventricular contractility and performance observed with administration of levosimendan. Systemic vasodilation decreases left heart filling pressures, enhances LV–arterial coupling, and increases blood flow to various tissues, including myocardium, gastric mucosa, renal medulla, small intestine, and liver. In the splanchnic area, levosimendan is superior to milrinone and dobutamine in selectively increasing microvascular gastric mucosal oxygenation and increases portal venous blood flow and oxygen delivery in experimental septic shock. Clinical consequences of levosimendan-induced vasodilation must be seen in context with the parallel improvement of cardiac performance. Although vasodilation may decrease mean arterial blood pressure, which compromises, for example, renal perfusion, the parallel increase in cardiac output frequently more than compensates this handicap. For example, renal function was improved after a 24-h infusion of levosimendan (0.1– 0.2 micg/ kg/ min) in patients with low-output heart failure as demonstrated by decreases of serum creatinine levels (9 M) compared with infusions of dobutamine (5–10 micg /kg/ min).

Anti-ischemic Effects of Levosimendan: Particularly during ischemia and reperfusion, administration of catecholamines and PDE III inhibitors produce detrimental side effects, *e.g.*, atrial and ventricular tachyarrhythmias. In this setting, availability of positive inotropic drugs with a neutral profile on cardiac rhythm and anti-ischemic effects would confer benefits.

KATP Channel Opening: Levosimendan opens both mitochondrial and sarcolemmal KATP channels. Although the definite relevance of these actions is unknown, opening of mitochondrial KATP channel has repeatedly been implicated in mediation of anti-ischemic actions. Prevention of mitochondrial Ca2 overload, restoration and stabilization of mitochondrial membrane potential, preservation of high-energy phosphates, and regulation of mitochondrial matrix volume have been proposed as underlying mechanisms. Interestingly, the positive inotrope levosimendan protected ischemic myocardium, decreased myocardial infarct size when administered before and during myocardial ischemia in dogs, and improved survival compared with placebo in patients with LV failure complicating acute myocardial infarction. Opening of sarcolemmal KATP channels, however, has been implicated in both mediating cardioprotective effects and exerting a theoretical proarrhythmic potential. This detrimental action on heart rhythm is produced by the large outward repolarizing K current that sarcolemmal KATP channel opening initiates. Subsequent hyperpolarization of resting membrane potential and shortening of action potential duration decreases the effective refractory period of the tissue and thereby increases the susceptibility to reentrant arrhythmias. Although levosimendan indeed hyperpolarized membrane potential, shortened action potential duration in isolated cells, and slightly shortened effective refractory period in patients,

experimental and clinical studies so far have demonstrated a neutral effect of this drug on heart rhythm rather than proarrhythmic potential.

Effects of Levosimendan during Ischemia, Stunning, and Myocardial Infarction: Because levosimendan does not increase myocardial oxygen demand and possibly exerts anti-ischemic effects, efficacy and safety of this substance have been intensively tested before, during, and after ischemia–reperfusion injury in experimental and clinical studies. Levosimendan did not promote ischemia–reperfusion arrhythmias compared with dobutamine in guinea pig hearts and in patients with stable moderate-to-severe ischemic cardiomyopathy when used in recommended clinical concentrations (6- to 24-micg/kg bolus over 10 min, followed by an infusion of 0.05– 0.2 micg /kg/min) in a double-blinded, placebo-controlled, randomized, multicenter study. Furthermore, the incidence of arrhythmias was not increased when levosimendan was compared with placebo in patients with acute myocardial infarction or administered perioperatively in patients with coronary artery bypass grafting. Although obviously having a neutral profile on heart rhythm, levosimendan consistently improved contractile function in the setting of global ischemia–reperfusion injury in experimental and clinical studies. In contrast, two experimental studies using regional myocardial ischemia in pigs demonstrated detrimental effects of levosimendan during ischemia, *i.e.*, increase in the rate of ventricular arrhythmias and worsening of the myocardial contractile function in the ischemic area. An increased frequency of ventricular arrhythmias was also noted at levosimendan doses of 0.6 mg/ kg/ min (*i.e.*, 3 times higher than upper recommended dose) in patients with stable ischemic cardiomyopathy. The reasons for these findings may be related to a decline in coronary perfusion pressure, redistribution of coronary blood flow producing coronary steal, and increase in myocardial oxygen consumption due to PDE III inhibition. Therefore, as with any other positive inotropic drug, caution is advised with the use of levosimendan, especially in high doses, in patients who have ongoing myocardial ischemia. Efficacy and safety of levosimendan have been demonstrated during states of myocardial stunning in experimental settings and in patients with acute coronary syndrome undergoing angioplasty in a randomized, double-blinded, placebo-controlled trial. Administration of levosimendan before or during myocardial stunning is of special interest not only because of the myofilament Ca2 sensitization of this drug. The decrease in myofilament responsiveness that characterizes stunning can also be prevented by ischemic preconditioning. Because opening of myocardial KATP channels plays a key role in the mediation of ischemic preconditioning, one may speculate that administration of the KATP channel opener levosimendan before ischemia may also prevent or attenuate the negative effects of myocardial stunning. Levosimendan also has cardioprotective effects by opening KATP channels in dogs with acute myocardial infarction. In this setting, levosimendan decreased myocardial infarct size while producing positive inotropic effects. These protective actions were blocked with glibenclamide without alteration of the hemodynamic effects of levosimendan.

Pharmacokinetics, Metabolism, and Dosage

Pharmacokinetics: Although during CHF pharmacokinetics of many drugs may be altered because of reduction of central volume, fluid retention, and reduced blood flow to various organs, including liver and kidneys, pharmacokinetic parameters of intravenous levosimendan are comparable when obtained in healthy volunteers and patients with mild or NYHA functional class III or IV heart failure. Levosimendan has a elimination half-life, volume of distribution, and total body clearance of approximately1 h, 20 l, and 300 ml/min, respectively. These parameters remain constant independent of the duration of infusion. Because levosimendan at a pH of 7.4 is present primarily in the ionized form (pKa 6.26) and is 98% bound to plasma proteins, only trace amounts of the unchanged drug are found in erythrocytes and urine.

Metabolism: The extensive metabolism of levosimendan yields biologically active metabolites (*e.g.*, OR-1855, OR-1896) that are eliminated in urine and feces. The clinically most relevant metabolite, OR-1896, also has Ca2-sensitizing and weak PDE III–inhibiting properties and exerts positive inotropic effects similar to the parent compound. OR-1896, however, has an elimination half-life of 80–96 h, reaches maximum plasma concentrations approximately 2 days after withdrawal of a 24-h infusionof levosimendan in patients with And is likely to be responsible for the sustained or greater hemodynamic effects observed after discontinuation of levosimendan. Because of this accumulation of OR- 1896, intravenous administration of levosimendan is therefore currently approved for 24 h. The effects of continuous infusions exceeding 24 h on plasma levels of levosimendan and its circulating metabolites and possible desired and undesired side effects, however, have recently been repeatedly investigated. Pharmacokinetics of levosimendan were similar after single-dose administration and continuous infusion of 7 days, whereas accumulation of OR-1896 was confirmed. An extended infusion of 0.1 mg /kg/ min over 7 days decreased systolic blood pressure (11- 14 mmHg) and substantially increased heart rate (19- 26 beats/min) on CHF (fig. 4).

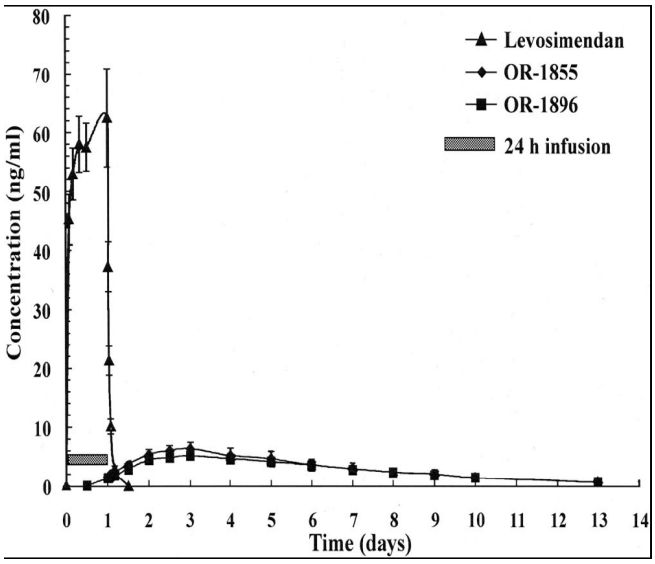


Fig. 4. Plasma concentrations of levosimendan and its metabolites, OR-1855 and OR-1896, during and after a 24-h infusion of levosimendan in patients with chronic heart failure. Concentrations of levosimendan decline quickly after discontinuation of the infusion, whereas both metabolites reach maximum plasma concentrations approximately 2 days after withdrawal of levosimendan. *Error bars* indicate SEMs. day 7 but was nevertheless well tolerated in patients with NYHA functional class III or IV symptoms of heart failure and ejection fractions below 40%.

Dosage: Administration of a 6- to 24-micg/kg bolus dose of levosimendan followed by a 24-h infusion of 0.05– 0.2 micg/ kg/ min produces plasma concentrations of 10–100 ng/ml (0.035– 0.35 M) in patients with NYHA functional class II–IV heart failure and can be considered as the therapeutic range to obtain favorable hemodynamic effects.

Safety Issues: Levosimendan generally is well tolerated by patients with moderate or severe heart failure, with an overall frequency of adverse events of 17–29%, which is similar to that of placebo (17–20%).

Interaction with Concomitant Heart Failure Drugs: In most clinical trials that evaluated the effects of levosimendan in heart failure, patients were taking concomitant routine heart failure drugs. For example, in a randomized multicenter trial, 89% of patients receiving levosimendan were using angiotensin-converting enzyme (ACE) inhibitors, 95% were using diuretics, 76% were using digoxin, and 37% were using blockers. Although additive responses particularly regarding vasodilation (*i.e.*, ACE inhibitors and levosimendan) and heart rate (*i.e.*, nitrates or blockers and levosimendan) would be expected, clinical studies so far have not reported serious interactions when levosimendan was used within the recommended dose range and in patients with myocardial contractile impairment. A subgroup analysis evaluating the concomitant effect of blockade on hemodynamics revealed no reduction of the effects of levosimendan on cardiac output and PCWP, whereas the actions of dobutamine were attenuated. This finding is in agreement with previous preclinical and clinical data demonstrating beneficial or neutral effects of parallel atenolol or carvedilol administration on the inotropic effects of levosimendan.

In another double-blinded, randomized, multicenter trial, the majority of patients received ACE inhibitors (5–20 mg enalapril), nitrates, and diuretics when various dose regimes of levosimendan were compared with dobutamine or placebo. Although no direct comparisons were made between patients with or without these drugs, treatment with levosimendan within the recommended doses (0.05– 0.2 micg/ kg/ min) in general was associated with only minor decreases in mean arterial blood pressure (2.8-3.5 mmHg) after 24 h of treatment. Similarly, 50 mg captopril did not further decrease systolic or diastolic blood pressures when administered concomitantly with levosimendan in patients with NYHA functional class II or III after previous myocardial infarction. Although no major additive hemodynamic effects of the combination of levosimendan and isosorbide-5-mononitrate compared with each drug alone were observed in healthy subjects at rest, an exaggerated circulatory response during an orthostatic test (*i.e.*, increase in heart rate by 40 beats/min; inability to stand upright) was observed with this combination of drugs. In contrast, concomitant nitrate therapy in patients with acute myocardial infarction produced only marginal decreases in systolic blood pressure (5 mmHg) and minor increases in heart rate (4 beats/min). Similarly, 5 mg felodipine, a dihydropyridine calcium antagonist, combined with oral levosimendan did not further increase heart rate and had no effect on blood pressure. No exaggerated or attenuated hemodynamic side effects of levosimendan were further reported in the presence of furosemide (10 mg/h) and amiodarone.

Hemodynamic Side Effects: Dose-dependent increases in heart rate and decreases in mean arterial blood pressure and total peripheral and pulmonary vascular resistance may cause a variety of unfavorable hemodynamic effects, including myocardial ischemia, hypotension, cardiac arrhythmias, and hypoxemia. Treatment within the recommended doses of levosimendan, however, does not induce myocardial ischemia and symptomatic or asymptomatic hypotension (10-mmHg pressure decrease). Levosimendan-induced vasodilation may, however, be responsible for the increased frequency of headache, dizziness, and nausea observed in several clinical trials.

Electrophysiologic Side Effects: Short-term intravenous administration (18-micg/kg bolus followed by 0.4 micg/ kg/ min) increases heart rate, shortens sinus node cycle duration and sinus node recovery time, and decreases atrioventricular nodal conduction interval and refractory periods. These actions indicate that levosimendan enhances impulse formation and conduction, accelerates the recovery of excitability, and therefore may also increase the ventricular response rate during atrial fibrillation. Several clinical studies including patients with atrial fibrillation, however, have been performed, and so far, no adverse effects related to this rhythm disorder have been reported. Levosimendan may prolong the rate-corrected QT interval(QTc), depending on dose, duration of administration, patient profile, and mode of calculation. When used in recommended doses (12 micg/kg over 10 min followed by an infusion of 0.05– 0.2 micg/ kg/ min), the Qtc interval remained unaffected. Single-bolus injections of 6.5 and 25 micg/kg without subsequent continuous infusion in healthy men produced Qtc prolongations as assessed by the Bazett equation of 6 ms and 21 ms, respectively. In contrast, administration of bolus doses of 24 and 36 micg/kg followed by continuous infusions of 0.4 and 0.6 micg/ kg/ min prolonged Qtc duration by 15 -20 and 10-45 ms in patients with NYHA functional class II–IV heart failure. Continuous infusions of levosimendan in doses of 0.05– 0.1 mg /kg/ min but over 7 days increased mean QTc values by 38-42 and 40-52 ms. The impact of this proarrhythmic potential of levosimendan must be weighed against possible antiarrhythmic actions due to the lack of cytosolic Ca2 accumulation, maintenance of diastolic coronary blood flow, and neutral effect on myocardial oxygen consumption. To date, there is no evidence of an increase in the development of new supraventricular or ventricular tachyarrhythmias,including torsade de pointes, in healthy volunteers and patients with severe heart failure, suggesting little potential for the drug to provoke life-threatening proarrhythmic reactions.

Other Side Effects: Serum potassium levels, erythrocyte count, and hemoglobin and hematocrit values may slightly decrease after prolonged levosimendan infusion, suggesting a routine control and correction of these parameters in clinical practice.

Clinical Trials with Possible Indications for Levosimendan: Currently, administration of levosimendan is approved for short-term treatment of acute decompensated CHF when conventional therapy with diuretics, ACE inhibitors, and digitalis is insufficient and inotropes are required. In addition, because of its interesting pharmacologic profile, several other possible indications for levosimendan have recently been explored, and the encouraging results of these trials may place levosimendan as a valuable expansion or replacement of standard therapy in the future.

Acute Decompensation of CHF: The LIDO study, a randomized, double-blinded, multicenter trial, compared the effects of levosimendan with dobutamine in 203 patients with acute decompensated low-output heart failure.These patients had an LV ejection fraction of less than 35%, a cardiac index of less than 2.5 l min1 m2, and a PCWP or 15 mmHg or greater on the basis of deterioration of severe CHF, heart failure after cardiac surgery, or acute heart failure related to a cardiac or noncardiac disorder of recent onset. Abolus of levosimendan of 24 micg/kg was infused over 10 min, followed by a continuous infusion of 0.1 micg /kg/ min for 24 h. Dobutamine was infused for 24 h at an initial dose of 5 micg /kg/ min without a bolus.

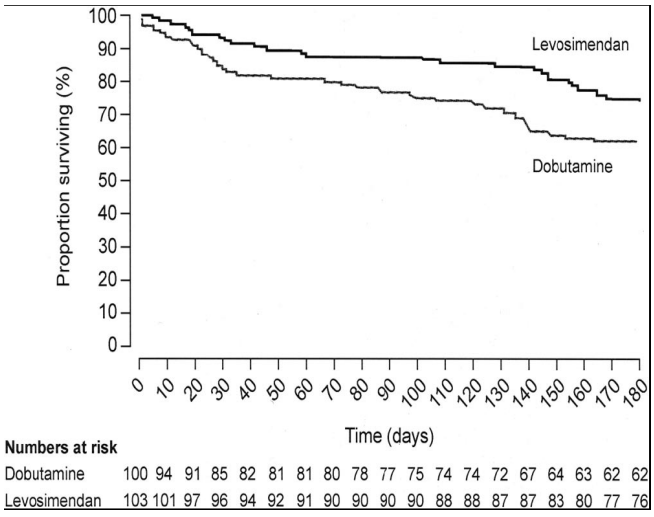


Fig. 5. Kaplan-Meier estimates of risk of death during 180 days after a 24-h infusion of levosimendan (0.1– 0.2 micg/ kg/min) or dobutamine (5–10 micg /kg/ min) in patients with lowoutput heart failure. Administration of levosimendan was associated with both a significantly lower 31-day (8% *vs.* 17%; *P* 0.045) and 180-day (26% *vs.* 38%; *P* 0.029) mortality. The infusion rate of each drug was doubled (*i.e.*, 0.2 micg / kg/ min levosimendan and 10 micg/ kg/ min dobutamine) if the response was inadequate at 2 h. The primary endpoint was the proportion of patients with hemodynamic improvement (*i.e.*, increase of cardiac output of 30% or more and decrease of PCWP of 25% ormore) at 24 h. All-cause mortality was assessed prospectivelyat 31 days and retrospectively at 180 days after randomization. Levosimendan treatment was superior to dobutamine in increasing cardiac output and decreasingPCWP (fig. 3), and a significantly greater proportion of patients in the levosimendan group achieved the primary endpoint compared with the dobutamine group(28% *vs.* 15%; *P* 0.022). Although overall frequency of adverse events was similar, headache tended to be associated more frequently with levosimendan, whereas rhythm disorders and myocardial ischemia were more common with dobutamine.

Administration of levosimendan was associated with both a significantly lower 31-day (8% *vs.* 17%; *P* 0.049) and 180-day (26% *vs.* 38%; *P* 0.029) mortality (fig. 5). Interestingly, levosimendan was equally effective in patients with concurrent -blocker therapy, whereas the actions ofdobutamine were attenuated, as expected. Interpretation of these encouraging results must include consideration that comparable hemodynamic effects might have also been achieved with higher infusion rates of dobutamine (although possibly with higher adverse events) and that, because of the lack of a placebo group, it cannot be derived whether this was a true beneficial effect of levosimendan or rather reflected a more adverse effect of dobutamine. Beneficial hemodynamic effects of levosimendan were also observed in a 6-h short-term treatment of 146 patients with acute decompensated ischemic or dilated cardiomyopathy in a multicenter, double-blinded, placebo-controlled trial. In these patients with NYHA functional class III or IV symptoms of heart failure and ejection fractions of 30% or less, levosimendan therapy was initiated with a bolus dose of 6 micg/kg, followed by a continuous infusion of 0.1 micg /kg/ min. At hourly intervals, a repeat bolus of 6 micg/kg was given, and the infusion rate was up-titrated by increments of 0.1mic g /kg/min until a maximum rate of 0.4 micg /kg /min was achieved or a dose-limiting event (*i.e.*, heart rate 130 beats/min or increase in heart rate of 15 beats/min, symptomatic hypotension or a decrease in systolic blood pressure to 75 mmHg, decrease in PCWP to 10 mmHg) occurred. The primary endpoint was the proportion of patients with an increase in stroke volume or a decrease in PCWP of 25% or more at 6 h. Levosimendan dose-dependently increased LV stroke volume (maximum 28% with the highest dose), cardiac index (maximum 39%), and heart rate (maximum 8%) and decreased PCWP (maximum 6 1 mmHg) when compared with placebo.

Inotropic Support during and after Myocardial Ischemia: Safety, efficacy, and effects on mortality of various doses of levosimendan were investigated in the RUSSLAN study, when this drug or placebo was administered in 504 patients with LV failure complicating acute myocardial infarction in a randomized, double-blinded, multicenter trial. In this investigation, four different dosing regimens of levosimendan were tested (6- to 24-micg/kg bolus infused over a period of 10 min, followed by 6 h infusions of 0.1– 0.4 micg /kg/ min). At the time of levosimendan administration, most patients were using nitrates and diuretics, approximately 40% were using ACE inhibitors or blockers, and 17% had received thrombolysis. None of the patients had received percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. In the highest dosing group (24micg/kg bolus followed by 0.4 micg/ kg/ min), a trend toward higher frequency of ischemia and hypotension was observed, but these effects were not evident at lower doses (0.1– 0.2 micg /kg/_ min). Levosimendan treated patients in general experienced a lower risk of death and worsening heart failure than patients receiving placebo during both the 6-h infusion (2.0% *vs.* 5.9%) and over 24 h (4.0% *vs.* 8.8%; *P* 0.044). Furthermore, all-cause mortality among levosimendan-treated patients was significantly lower than with placebo for the 14-day period after the start of treatment (11.7% *vs.* 19.6%; *P* 0.031) and exhibited a trend toward reduced mortality after 180 days of follow-up (22.6% *vs.* 31.4%; *P* 0.053).This study suggests that levosimendan infusions of 0.1– 0.2 micg /kg/ min are favorable compared with higher doses, because they combine a low potential of side effects with a maintained positive effect on survival in patients with LV failure complicating acute myocardial infarction Although levosimendan also produced significantly fewer ischemic adverse side effects compared with dobutamine in the LIDO study, did not aggravate ischemia in patients with stable coronary heart disease as assessed by a 24-h Holter electrocardiogram, and enhanced cardiac output in patients with ischemic heart disease and LV dysfunction,caution may be advised when this drug is administered in patients with critical coronary stenoses and regional myocardial ischemia.

In this setting, despite improvement of overall contractile function, animal experiments demonstrated detrimental effects of levosimendan that may have been due to declines in coronary perfusion pressure producing failure of autoregulation, coronary steal, or increased mechanical stress of myocytes between ischemic and nonischemic areas.

Myocardial Stunning after Percutaneous Transluminal Coronary Angioplasty in Patients with Acute Coronary Syndrome: Improvement of the function of stunned myocardium after percutaneous transluminal coronary angioplasty was shown after infusion of levosimendan in 24 patients with acute coronary syndrome in a double-blinded, randomized, placebo-controlled trial. Levosimendan (24micg/kg over 10 min) was administered 10 min after successful coronary angioplasty, and LV and regional functions were assessed by pressure–volume loops and Slager wall motion analysis, respectively. In levosimendan-treated patients, systolic function improved and the number of hypokinetic segments decreased from 8.9 1.0 to 6.5 1.1 when compared with placebo (7.8 1.0 to 8.5 1.1). This action occurre without parallel impairment of diastolic function.

Cardiac Surgery: Although the efficacy of levosimendan has repeatedly been demonstrated in the perioperative setting, the number of patients investigated was rather small. In a randomized, double-blinded, placebo-controlled study, levosimendan (18- or 36-micg/kg bolus and 0.2- or 0.3-micg /kg/ min infusion) administered 15 min before separation of cardiopulmonary bypass and continued for 6 h had beneficial effects on cardiac performance in low-risk patients and had no detrimental effects on arterial oxygenation and perioperative arrhythmias. In this study, administration of the 36micg/kg bolus instantly increased heart rate, although this effect vanished after 1 h despite continuation of the infusion. Similarly, levosimendan (8 or 24 micg/kg administered as a 5-min bolus without continuous infusion) improved hemodynamic parameters without changing myocardial oxygen consumption or substrate extractions after coronary artery bypass grafting in patients with ejection fractions greater than 30%. The high dose but not the low dose of levosimendan increased heart rate (maximum 11 beats/min) during the observation period of 1 h. In the setting of off-pump coronary artery bypass surgery, increases in stroke volume and cardiac output and decreases in systemic vascular resistance were observed when levosimendan was administered in two different bolus doses (12 or 24 micg/kg over 10 min) 20 min before the start of surgery in patients with normal preoperative ventricular function. Heart rate increased in both levosimendan-treated groups during the observation period of 1 h, whereas no differences in mean arterial blood pressure were demonstrated compared with placebo.

Levosimendan in Cardiac Surgery: AUnique Drug for the Treatment of Perioperative Left VentricularDysfunction or Just Another Inodilator

Searching for a Clinical Application: The myofilament calcium (Ca2) sensitizers are a class of positive inotropic, vasodilating drugs ("inodilators") that augment myocardial contractility by increasing the Ca2 sensitivity of the contractile apparatus without altering intracellular Ca2 concentration. Ca2 sensitizers (including levosimendan, pimobendan, sulmazole, EMD 57033, and MCI-154) have received considerable attention for the treatment of acute and chronic congestive heart failure because, unlike 1-adrenoceptor agonists or cardiac phosphodiesterase (PDE) III inhibitors that stimulate cyclic adenosine monophosphate (cAMP)-mediated signaling and increase intracellular Ca2 concentration, these drugs do not adversely affect myocardial oxygen supply-demand relations ,produce cardiotoxicity, or predispose to the development of arrhythmias. Levosimendan was developed over a decade ago, and based on a large body of accumulated experimental and clinical evidence, appears to be the most promising of these drugs. Levosimendan has already been approved for the treatment of acute exacerbation of chronic heart failure in several European countries following European Society of Cardiology guidelines.

The drug is currently undergoing Phase III clinical trials in the United States (REVIVE study) to evaluate its utility for the acute or chronic management of heart failure, and has received "fast-track" status from the Food and Drug Administration. The mechanisms by which levosimendan enhances the inotropic state and produces vasodilation have been extensively studied. Briefly, levosimendan binds to the regulatory protein troponin C (TnC) and stabilizes the Ca2-bound conformation of TnC, thereby allowing unopposed interaction between actin and myosin filaments and enhancing the rate and extent of myocyte contraction. A unique feature of levosimendan-TnC binding is its dependence on intracellular Ca2 concentration that facilitates the interaction between TnC and Ca2 during systole, while simultaneously allowing Ca2 to dissociate from the protein during diastole. This Ca2-dependence of TnC binding prevents deleterious abnormalities in relaxation that would otherwise be expected to occur. Preservation of lusitropic function is also facilitated by the PDE-inhibiting properties of levosimendan that occur at higher doses of the drug.

Levosimendan-induced systemic, pulmonary, and coronaryvasodilation occurs as a result of at least three distinct mechanisms. Levosimendan opens several types of potassium (K) channels (including voltagedependent, ATP-sensitive, and Ca2-activated forms) in conductance and resistance vessels, actions that reduce intracellular Ca2 concentration in vascular smooth muscle. Levosimendan induces Ca2 desensitization of the contractile apparatus in vascular smooth muscle that does not contain TnC independent of intracellular Ca2 concentration. PDE inhibition may also play a role in vasodilation produced by higher doses of the drug. Unlike other inotropic drugs, levosimendan may exert important antiischemic effects by virtue of its actions as a KATP channel opener. Levosimendanactivates sarcolemmal and mitochondrial KATP channels *in vitro*, and these channels play a critical role in myocardial protection against reversible and irreversible ischemic injury. Levosimendan reduced myocardial infarct size in a canine model of ischemia and reperfusion *in vivo*, independent of alterations in systemic hemodynamics or coronary collateral blood flow, and this beneficial action was abolished by the nonselective KATP channel antagonist glyburide. Levosimendan enhanced the functional recovery of stunned myocardium after percutaneous transluminal coronary angioplasty in patients with acute myocardial ischemia and was also beneficial for the treatment of cardiogenic shock resulting from stunning of border zone myocardium during infarction. Brief administration of levosimendan to patients undergoing coronary artery bypass graft surgery before cardiopulmonary bypass was associated with lower postoperative troponin I concentrations. These latter data suggested that levosimendan may be capable of

producing pharmacological preconditioning in humans, presumably as a consequence of its actions on the KATP channel. The clinical efficacy of levosimendan in patients with heart failure resulting from ischemic heart disease, dilated cardiomyopathy , and acute myocardial infarction has been well documented. Levosimendan causes dose-dependent improvements in systemic and pulmonary hemodynamics in patients with heart failure concomitant with a reduction in clinical symptoms ; but the myofilament Ca2 sensitizer does not produce hypotension, exacerbate ongoing ischemia,or contribute to mortality by increasing the incidence of arrhythmias. In contrast, a major clinical trial of the PDE III inhibitor, milrinone, in patients admitted for an acute exacerbation of chronic heart failure demonstrated that milrinone did not alter inhospital or 60-day mortality when compared with placebo, caused more frequent episodes of hypotension requiring intervention, and increased the incidence of arrhythmias as compared to placebo. When compared with the -adrenoceptor agonist, dobutamine, levosimendan also produced more favorable alterations in hemodynamics and reduced mortality in patients with low-output heart failure and in those with cardiogenic shock after percutaneous coronary intervention.

The relative superiority of levosimendan when compared with dobutamine described in these studies may be related to the antiinflammatory and antiapoptotic effects of the myofilament Ca2 sensitizer. Similar to the findings in the setting of heart failure,levosimendan has also been shown to increase cardiac performance concomitant with reductions in pulmonary capillary occlusion pressure and systemic vascular resistance in patients with normal and depressed left ventricular (LV) function undergoing cardiac surgery with or without cardiopulmonary bypass. In the current issue of *Anesthesia & Analgesia*, De Hert et al. provide further evidence that levosimendan produces beneficial hemodynamic effects inpatients with preoperative LV dysfunction (ejection fraction 30%) undergoing cardiac surgery who required inotropic support after cardiopulmonary bypass. Despite the inherent problems associated with a strict comparison between drugs of differing pharmacological action and relative potency, the authors demonstrate that the combination of IV infusions of levosimendan (0.1 micg/ kg/ min) and dobutamine micg /kg/ min) produces very similar cardiovascular effects to those observed with the combination of milrinone (0.5 micg/ kg/min) and dobutamine during the first 24 h after cardiopulmonary bypass. The data further suggest that levosimendan-dobutamine may augment stroke volume index to a greater degree than milrinone-dobutamine 12 and 24 h after bypass, although these results may most likely be attributed to the greater reductions in systemic vascular resistance observed in patients receiving the combination of levosimendan and dobutamine. Loading doses of levosimendan or milrinone were not administered, but infusions of these drugs were initiated upon removal of the aortic cross-clamp preceding a prolonged reperfusion before separation from bypass. Thus, steady state plasma concentrations of levosimendan and milrinone were probably established before bypass was discontinued. Perhaps of more importance, the results indicate that the total doses of dobutamine and norepinephrine (used to treat mean arterial blood pressure 60 mm Hg) required during the first 48 h after cardiopulmonary bypass, the total duration of inotropic drug treatment, the duration of mechanical circulatory support (intraaortic balloon counterpulsation was required in four of 15 patients per group), and time to tracheal extubation were significantly less in patients receiving levosimendan-dobutamine when compared with those treated with milrinone-dobutamine. The beneficial hemodynamic effects of levosimendan have been shown to persist for at least 24 h after discontinuation of continuous infusion as a result of a biologically active metabolite (OR-1896) , and it is likely that the accumulation and prolonged effect of this metabolite may, at least partially, account for these dramatic differences between levosimendan- and milrinone-treated patients.

PDE III inhibitors such as milrinone have been a mainstay in the pharmacological management of LV dysfunction after cardiopulmonary bypass for many years. These drugs are commonly used in combination with 1-adrenoceptor agonists to provide a synergistic positive inotropic effect in the presence of bypassinduced down regulation of the 1-adrenoceptor and dysfunctional adenylyl cyclase-mediated signal transduction. Because the mechanism of action of levosimendan is not dependent on this signaling pathway, the drug may have the distinct advantage of enhancing myocardial contractility by acting directly at the level of the contractile apparatus. In addition, levosimendan may reduce the development of arrhythmias and the incidence of cardiotoxicity that often occur with other clinically used inotropic drugs, because increases inintracellular Ca2 concentration do not occur with the myofilament Ca2 sensitizer at typical therapeutic doses. KATP channel-mediated antiischemic effects and prolonged drug action resulting from an active metabolite also represent potentially important benefits of levosimendan in patients with LV dysfunction after cardiac surgery. Thus, the recent findings of De Hert et al. are certainly promising, and support the work of previous investigations. Nevertheless, PDE III inhibitors and 1-adrenoceptor agonists have a wellestablished record of clinical efficacy in the treatment of perioperative LV dysfunction. Given the success of these drugs in this setting, a fundamental question remains: Is another positive inotropic drug with vasodilating properties truly required to successfully treat these patients? Thus, whether the theoretical advantages of levosimendan will ultimately translate into improved outcome incardiac surgical patients with LV dysfunction is unknown and will require additional investigation to define.

Preconditioning effects of levosimendan in coronary artery bypass grafting- a pilot study: This pilot study demonstrates that pharmacological preconditioning with a short duration infusion of levosimendan in cardiac surgical patients before commencing CPB appears to confer additional myocardial protection beyond that provided by cardioplegia alone, as manifested by a better haemodynamic recovery and lower postoperative TnI levels. Preconditioning is classified into two distinct components: classic, early preconditioning and delayed or late preconditioning. Each has its own biological mechanism. Early cardioprotection is highly effective but relatively short-lived, whereas the delayed form of adaptation is manifested sub-acutely approximately 24 h following the preconditioning stimulus; its degree of protection is usually less than that achieved by early preconditioning, but its duration is considerably longer (72 h). Recent evidence suggests that in addition to enhanced tolerance to lethal ischaemic injury, delayed preconditioning confers protection against other end-points of ischaemia–reperfusion injury including ventricular arrhythmias and post-ischaemic myocardial dysfunction (stunning). The ATP-sensitive potassium (KATP) channel has been shown to be an important

mediator and/or end-effector of cardioprotection. Its role in early and late preconditioning has been demonstrated in whole animals, isolated hearts and in cardiac myocytes. Although some data suggest a critical role for the sarcolemmal KATP channel, most evidence to date is consistent with mitochondrial rather than surface channels as being more important. Evidence derived from animal models demonstrates that levosimendan, through its KATP channel opening properties, can mimic ischaemic preconditioning, and improve cardiac function and cell viability. The above-mentioned animal models have the limitation of being a partial ischaemia–reperfusion model; thus, a protective anti-ischaemic effect related to a levosimendan-induced increase in coronary blood flow cannot be excluded. Moreover, in such studies, a major confounding factor is the acute recruitment of collateral vessels.

Aortic cross-clamping performed during CABG induces a period of global ischaemia that excludes the recruitment of collateral vessels. Ours is the first study, albeit preliminary, that has investigated levosimendan-induced myocardial protection in humans with ischaemic heart disease undergoing a major cardiac and circulatory insult. Cardiac TnI release is a recognized marker of myocardial damage. Some studies suggest that troponin could be an early marker of postoperative myocardial ischaemia and infarction in cardiac surgery; although, in this setting, the use of cardiac specific markers for diagnosis and quantitation of myocardial damage is still debated. In our study, TnI was lower in the levosimendan group, a finding consistent with a beneficial cardioprotective effect. In the control group TnI levels are, however, similar to those previously reported in patients classified as having minor myocardial damage after coronary bypass grafting. The peak value (6.3 ng ml–1) observed at 6 h after operation in our series is much lower than the cut-off value (13.4 ng ml–1) that could differentiate between patients with myocardial infarction or ischaemia. Nevertheless, even in the perioperative scenario of limited myocardial damage, levosimendan appeared to offer cardioprotection.

Myocardial stunning plays a pivotal role in postoperative myocardial dysfunction. It represents a prolonged post-ischaemic contractile dysfunction of myocardium salvaged by reperfusion. Studies have demonstrated contractile dysfunction over the first few hours after myocardial revascularization19 that generally resolves spontaneously over 24–48 h and is independent of preload and afterload. Our results do not reflect this phenomenon. The CI increased over time in both groups (control after postop 6), albeit more so in the levosimendan group. As preload and afterload indicators were almost identical between the two groups, the haemodynamic improvement brought about by levosimendan was mostly related to myocardial protection. There is a limitation in using CI to evaluate the benefit derived from preconditioning as this variable could be influenced by the patient's preload and afterload, and inotropic requirements. Three of the twelve control patients required inotropes as opposed to one patient in the levosimendan group. Reported kinetics for levosimendan would exclude the haemodynamic benefit being derived from its calcium-sensitizing effect. The dosage used and the mode of administration in our study would not achieve either a minimum effective concentration of the drug nor appreciable amounts of its active metabolite OR-1896.23 Kinetic models have not yet considered the potential influences of hypothermia or CPB; however, this low dose of levosimendan (or its metabolite) is very unlikely to exert any haemodynamic effect at 24 h. This pilot study was designed to provide preliminary data to test the hypothesis that levosimendan has a preconditioning effect in patients. It was not fully blinded for logistical reasons; although the medical and nursing staff caring for the patients, and the research assistants collecting data were unaware of the randomization schedule. Our study provides no information on the dose-range of levosimendan relative to its cardioprotective effects. Previous studies suggest that a minimum duration of ischaemia is required to activate the endogenous preconditioning response,and that a certain threshold of stimulation has to be reached. Our study shows that a 24 μg kg–1 i.v. bolus of levosimendan may reach this preconditioning threshold. Further investigation is required to discover whether lower doses have the same efficacy in myocardial protection.

The general trend of reduced postoperative complications with levosimendan include a lower incidence of atrial fibrillation, less need for inotropic support, less time on the ventilator, and shorter ICU and hospital stays. Statistical significance was not achieved because of the small sample size, though this study was a hypothesis-generating pilot trial and not designed to assess outcome benefit, as has been reported with prolonged infusion of levosimendan in patients with decompensated heart failure. De Hert and colleagues demonstrated that the use of a cardioprotective halogenate-based anaesthetic regimen resulted in shorter intensive care and hospital length of stays. This seems to be related to better preservation of early postoperative myocardial function. Similar protective effects were obtained using sevoflurane in patients undergoing on-pump CABG. Garcia and colleagues found that preconditioning CABG patients may improve long-term cardiovascular outcomes, while Julier and colleagues also found improved renal function in a similar group of high-risk patients. The anaesthetic regimen and amounts used in our study were well-matched between levosimendan and control groups. Baggish and colleagues showed a positive correlation between postoperative troponin T levels and intensive care length of stay. The beneficial trends seen in outcome variables and lower TnI concentrations recorded in our levosimendan-treated patients are in agreement with the aforementioned studies and could be used to adequately power future trials.

A power analysis performed on the basis of this study suggests a sample size requirement of 96 patients (48 in each group) would be needed to detect a reduction in median ICU length of stay from 35 h in the control group to 24 h in the protocol group (=0.05, power 0.9). This further trial is currently underway in our hospital. In conclusion, this pilot study indicates that a short, 10 min infusion of levosimendan before commencing CPB, in patients with stable angina undergoing revascularization, results in improvements in haemodynamic performance and a reduction in TnI release. These data are consistent with a preconditioning effect in humans. Levosimendan may improve survival in patients requiring mechanical assist devices for post-cardiotomy heart failure. In this retrospective observation, we were able to demonstrate a positive effect of levosimendan on 180-day survival rates in patients with severe post-cardiotomy heart failure. The group of patients treated with levosimendan required less epinephrine in the postoperative period, showed lower plasma lactate concentration after explantation of the assist device, and significantly shorter duration of renal replacement therapy. No difference was found between the groups regarding the

incidence of acute renal failure as well as ICU or hospital length of stay. The survival rates in the conventional treatment group were similar to those reported by other centres; 10 studies observing the therapy with assist device implantation as a bridge to recovery showed that weaning was possible in 49% to 71% and discharge from hospital in 22% to 52% of patients. In our study, 69% of the patients in the conventional therapy group were able to be weaned from the assist device and 24% were finally discharged from hospital. In contrast, all of the patients in the levosimendan group were successfully weaned and 89% could be discharged from hospital. We have taken into consideration that the patients in the levosimendan group were of significantly younger age than those in the conventional treatment group. The average age of the patients in the levosimendan group was 57 years and ranged between a minimum of 45 years and a maximum of 68 years. This corresponds with an average age of 59 years published in other studies.

Not many data exist on long-term survival rates of patients receiving an assist device secondary to severe post-cardiotomy cardiac shock. Hoy and colleagues have reported 62 cases with implanted centrifugal pumps. In that study, of the observed patients were able to be discharged from hospital, 9 died in the first year after discharge, 10 further survived for less than 5 years, 7 survived for 6 to 10 years and 1 patient survived for more than 10 years after the procedure. The advantageous effects of levosimendan in patients with acute decompensated cardiac failure have been demonstrated in clinical trials. The multicenter RUSSLAN study investigated levosimendan in three different dosages versus placebo in patients with acutely impaired cardiac function due to myocardial infarction. The higher dosage of levosimendan (bolus 24 μg•kg-1 followed by infusion of 0.4 μg•kg-1•min-1) was associated with increased incidences of hypotension and ischemia compared to patients who received a bolus of 24 μg kg-1 followed by infusion of 0.2 μg × kg-1 × min-1 or patients who received a bolus of 12 μg kg-1 followed by infusion of 0.2 μg × kg-1 × min-1 or patients who received a bolus of 6 μg kg-1 followed by infusion of 0.1 μg × kg-1 × min-1.

The total number of levosimendan treated patients showed a significantly reduced 14-day mortality ($p = 0.031$) and the 180-day mortality tended to be lower in the levosimendan groups ($p = 0.053$). The multicenter LIDO study investigated levosimendan versus placebo in patients with acute decompensated heart failure; 180-day survival was significantly improved in the levosimendan group ($p = 0.029$). No controlled studies have ever examined the effect of levosimendan administration in cardiac surgical patients with severe impairment of ventricular function. Lehmann and co-workers reported 10 patients with severe cardiogenic shock undergoing emergency coronary artery bypass grafting (CABG). These patients were treated with levosimendan. Two patients died and eight patients showed an excellent clinical outcome without further complications. One study showed a significant improvement of hemodynamic measurements in patients undergoing CABG surgery with normal ventricular function. Morelli and co-workers showed that levosimendan improved the left ventricular stroke work index in septic patients with reduced ventricular function compared to patients treated with dobutamine. The authors observed no difference in norepinephrine dosages between the groups. Their patients were treated with optimal fluid loading. In our retrospective analysis, we also found no increase in administered norepinephrine dosages in levosimendan treated patients. In Morelli's study, levosimendan led to an increase in gastric mucosal blood flow, creatinine clearance, and urinary output. The authors found decreased troponin and lactate concentrations in levosimendan treated patients. In our retrospective observation, the duration of renal replacement therapy was significantly lower in the levosimendan group compared to the conventional therapy group. This could be due to improved renal perfusion. The significantly lower plasma lactate concentration following device explantation in levosimendan treated patients could possibly be an indicator for improved splanchnic perfusion and for protection of organs from ischemia/reperfusion injury through opening of ATP-dependent potassium channels by levosimendan. Another explanation for this finding could be a reduced administration of epinephrine in the levosimendan group. Epinephrine itself may lead to impaired splanchnic perfusion and metabolic alterations resulting in hyperlactatemia.

The Vasodilatory Effects of Levosimendan on the Human Internal Mammary Artery: The current study shows that levosimendan, a myofilament calcium sensitizer, effectively reversed thromboxane A2 analog and norepinephrine-induced contraction of IMA segments *in vitro*. The vasodilator effect is not dependent on the presence of endothelium. Levosimendan also exerts a potent, concentration dependent, inhibitory effect on IMA norepinephrine mediated contraction. Levosimendan, nitroglycerin, and milrinone reversed both norepinephrine- and thromboxane A2 analog-induced contractions. Judging from their EC50 values, levosimendan and milrinone appeared to have comparable potency for this effect. Based on similarcomparisons, nitroglycerin was significantly more potent in reversing norepinephrine and thromboxane A2 vasoconstriction. The EC50 for vasorelaxation of preconstricted IMA rings for levosimendan in our study (4.89 to 7.07 106 mol/L) was higher that the therapeutic level reported in patients (1.24 107 mol/L). This value corresponds to a relaxation of approximately 40%–50% in our study. Our results are in agreement with other's studies which have reported that nitroglycerin is more potent than other drugs for reverting precontracted IMA.

The mechanism of action of nitroglycerin is because of the release of nitric oxide resulting in activation of guanylate cyclase and increased formation of cyclic guanosine monophosphte leading to smooth muscle relaxation. The EC50 for this effect of nitroglycerin found in the present study is in the therapeutic range (109 to 108 mol/L) reported for this drug and comparable to the EC50 for nitroglycerin reported in other studies. A clinical limitation with nitroglycerin, though, is the development of tachyphylaxis, limiting its usefulness for long durations or for patients chronically treated with this drug before surgery. Consequently, different drugs have been evaluated as an alternative to nitroglycerin. Milrinone is a bypyridine derivative that selectivelyinhibits phosphodiesterase type III and prevents the degradation of cyclic adenosine monophosphate. Liu et al. investigated the effects of milrinone on IMA segments and established that it produces a potent endothelium-independent relaxation on the IMA. The data of the present study show an EC50 in the range of 2.1 to 4.9 106 mol/L; similar to the optimal therapeutic plasma concentration clinically reached and similar to that previously demonstrated in *in vitro* vascular ring studies. Despite the beneficial clinical myocardial inotropic and vasodilatory effects on the pulmonary and systemic

vasculature that both enhance right and left ventricular stroke volume, a rate-limiting factor for milrinone administration can increase myocardial oxygen demand with consequent risk for ischemia and arrhythmia. Levosimendan enhances the contractile force of myocardium by binding to troponin C without increasing the intracellular calcium concentration at therapeutic doses. In another cellular action, levosimendan promotes vasodilation by opening the ATPsensitive K channels. De Witt et al. showed that responses to levosimendan are reduced, yet not completely blocked, by KATP-channel blockers; this observation suggests that additional mechanisms may be involved in mediating the smooth muscle response to levosimendan. *In vitro* levosimendan has been found to be a highly selective inhibitor of phosphodiesterase; however, at concentrations exceeding the pharmacologically relevant concentrations for inducing positive inotropic effects.

After levosimendan infusion, the resultant venous and arterial dilation reduces cardiac preload and postload, improves oxygen supply to the myocardium, and enhances the renal blood flow. Such vasodilation by levosimendan is also thought to underlie the reductions in infarct size and myocardial ischemia as well as afford anti-myocardial stunning benefits. The results of this study suggest that levosimendan might have other beneficial clinical effects for preventing or treating IMA vasospam. There are promising human studies and clinical experience with levosimendan in cardiac surgery. The preliminary data in these relatively small studies suggest that levosi-mendan may be beneficial in low cardiac output states after cardiopulmonary bypass. In both studies, levosimendan increased cardiac output, heart rate, and decreased systemic and pulmonary vascular resistance. Despite improved cardiac performance, levosimendan did not increase myocardial oxygen consumption or change myocardial metabolism. Potential disadvantages of levosimendan include its association with arterial hypotension and its relatively high cost.

Some of the factors contributing to the development of IMA spasm include endogenous and exogenous catecholamines acting via -adrenoreceptors and other mediators, such as endothelin and thromboxane A2. In this study, the selection of two receptor agonists, norepinephrine and thromboxane A2 analog, as contracting agents was made because they are likely to play an important role in producing IMA-graft spasm in patients undergoing myocardial revascularization surgery. Plasma levels of those two vasoconstrictors are increased during and after conventional coronary artery bypass surgery and they may act synergistically in producing perioperative vasospasm. Our findings might have relevance to the care of patients who receive arterial grafts and have suspected vasospasm. However, as shown in the figures, there is a considerable variability in vasodilator effects among the vessel segments. Consequently, the EC50 value might not be correlated with the dose leading to an expected vasodilator effect *in vivo*. At present, there are little quantitative clinical data clearly supporting the use of a specific drug as a preventive strategy for postoperative IMA spasm. Nitroglycerin, although effective in reversing established spasm, may be much less effective if it is given before the constrictor stimulus. In our study, when added as pretreatment, levosimendan antagonized norepinephrine-induced vasoconstriction. This suggests a prophylactic role for calcium sensitizers, such as that has been reported for drugs acting through receptor-operated calcium channels, such as nifedipine, and the phosphodi-esterase III inhibitor milrinone. Although effective for reversing or preventing vasoconstriction of IMA segments, these effects might not be observed in other arterial bypass graft conduits, such as the radial artery. Differences between the radial artery and IMA to a contractile agonist have been reported, with the radial artery showing a stronger contractile response than the IMA. In addition, there may be differences between the two arteries in the mechanisms underlying vasodilation. Thus, the optimal treatment to attenuate vasospasm may not be identical for the two vessels. Postoperative saphenous venous spasm is a rarity, and can be readily reversed by nitroglycerin. However, spasm of the saphenous vein during harvesting is a common phenomenon that can be minimized by careful surgical technique. Future studies are necessary in order to investigate the vasodilator effects of levosimendan on other arterial conduits and the saphenous vein. In conclusion, our results indicate that levosimendan is a potent, endothelium-independent vasodilator of human IMA. In light of its positive inotropic and vasodilator properties, levosimendan might be beneficial for the perioperative treatment of patients undergoing coronary artery bypass grafting.

Effect of levosimendan on myocardial contractility, coronary and peripheral blood flow, and arrhythmias during coronary artery ligation and reperfusion: Levosimendan is a unique calcium sensitiser that binds to myocardial troponin C and facilitates the activation of the contractile apparatus by calcium. In addition, levosimendan opens the ATP sensitive potassium channel in both vascular smooth muscle and ventricular myocytes. A previous study from our laboratory showed that levosimendan improved reperfusion function without increasing the incidence of arrhythmias in the isolated guinea pig model of global ischaemia. In the present study, using an in vivo large animal model, levosimendan increased ischaemic and reperfusion cardiac output and preischaemic and reperfusion left ventricular contractility (LVmaxdP/dt). However, it also increased the number of arrhythmic events during ischaemia in this model of regional ischaemia.

Levosimendan increased coronary flow and decreased systemic vascular resistance throughout the study. These secondary vasodilator properties would be expected to produce further improvement in ischaemic and reperfused function by virtue of their anti-ischaemic affects in the heart. Because the ischaemic myocardium copes poorly with raised calcium concentrations (either intracellular or extracellular), calcium sensitisers could be particularly effective in the treatment of the ischaemic and reperfused heart. These compounds do not increase the already raised calcium concentrations in the ischaemic myocardium, and this would be expected to reduce the risk of further exacerbating the cytosolic calcium overload induced by ischaemia and reperfusion. Calcium sensitisers should also be electrophysiologically “silent”—that is, they should not cause electrophysiological manifestations that may predispose the heart to arrhythmias.

Haemodynamic changes induced by levosimandan: Levosimendan improved cardiac output both during ischaemia and reperfusion in this study. This increase in cardiac output is probably a result of improved contractility (left ventricular dP/dt) and a reduction in systemic vascular resistance in the levosimendan treated animals. Despite the fact that

levosimendan did not increase contractility during ischaemia, stoke volume was higher in levosimendan treated hearts than in the placebo group. This increase in stroke volume was not caused by a reduction in heart rate in these animals. The difference in stroke volume between the two groups is because of an ischaemia induced decrease in stroke volume in the placebo hearts. Levosimendan treatment prevented this ischaemia induced reduction in stroke volume observed in the placebo treated animals. Contractility (LVmaxdP/dt) is an index of velocity of contraction and is largely independent of the preload/systemic vascular resistance to which the heart is subject. In this study, LVmaxdP/dt was at its lowest shortly after reperfusion under control conditions. Levosimendan, however, greatly improved the contractility of the heart early in reperfusion. These data support our proposal that the improved cardiac output observed with levosimendan treatment is not merely the result of a decreased systemic vascular resistance, but also reflects improved contractile function of these hearts. These results confirm our earlier findings in an isolated guinea heart model.

Vasodilator properties of levosimendan: A pronounced coronary and peripheral vasodilator effect of levosimendan has been described in previous studies. Recent electrophysiological studies with levosimendan suggest that these vasodilator effects are mediated through opening of the ATP sensitive potassium channel in vascular smooth muscle cells.These vascular effects of levosimendan would be expected not only to increase blood flow to the underperfused myocardium, but also to reduce the afterload on the heart. The aim of various haemodynamic treatments used in heart failure is to reduce the afterload on the heart, which would be expected to improve myocardial performance by allowing better left ventricular emptying, reducing end diastolic volume, and consequently reducing end diastolic preload.

Levosimendan and ventricular arrhythmias: A major concern with the clinical use of conventional inotropic agents has been that they tend to be proarrhythmic, possibly because they promote the formation of tissue cAMP, either by â adrenergic stimulation or by phosphodiesterase inhibition. Because only high concentrations of levosimendan (more than 90 ng/ml) are thought to inhibit phosphodiesterase-III, we believe that inhibition of phosphodiesterase activity by levosimendan can be ruled out in our study as plasma concentrations never exceeded 30 ng/ ml. In addition, although tissue cAMP concentrations were raised in the ischaemic region of the levosimendan treated hearts, this increase was similar in both treatment and control groups. The ischaemia induced increase in tissue cAMP is a well described phenomenon not yet fully understood. The effect of levosimendan on the incidence of arrhythmias has been reported in a limited number of studies such as ours and that of Nijhawan and colleagues, in conditions where hearts were subjected to global ischaemia. In both studies levosimendan was found to have no effect on the incidence of arrhythmias, either during ischaemia or reperfusion. The difference in the effect of levosimendan on the incidence of ischaemic arrhythmias observed in this study may be explained by the difference in the models of ischaemia. We know that hearts subjected to regional ischaemia are more prone to arrhythmias owing to the inhomogeneity of the myocardium over the ischaemic and non-ischaemic zone of these hearts.

Myocardial metabolism: The increase in blood flow to the ischaemic zone by levosimendan would be expected to reduce ischaemic damage by preserving the energy status of the heart. In addition, opening of the ATP sensitive potassium channel has been linked to an increase in tissue viability. In this study, however, tissue ATP and phosphocreatine contents remained unchanged. Our results are in contrast with those obtained in two other studies where levosimendan reduced ischaemic damage as measured by epicardial nicotinamide adenine dinucleotide phosphate (NADH) fluorescence photography and high energy phosphate compounds. The reason for this may be the severity of ischaemia in the pig heart following coronary artery ligation.Despite the levosimendan induced improvement in blood flow to the peripheral ischaemic zone (during ischaemia), residual blood flow was only about 12% of the preligation value.

Cardiogenic Shock: In the presence of refractory cardiogenic shock (definedas cardiac index 2.2 l min1 m2, PCWP 16 mmHg, systolic blood pressure90 mmHg,and requirement of catecholamines), 0.1 micg kg1 min1 levosimendan for 24 h as add-on therapy favorably altered hemo-dynamic parameters by increasing cardiac index from 1.8 0.4 to 2.4 0.6 l min1 m2 and decreasing systemic vascular resistance from 1,559 430 dyn · s · cm5 to 1,109 202 dyn · s · cm5, although it was administered without administration of a bolus in 10 patients. No significant changes in mean arterial blood pressure (78 mmHg to 73 mmHg), heart rate (96 to 101 beats/min), or adverse events were observed in this uncontrolled, retrospective study. Similarly, in a case series of 10 patients with cardiogenic shock undergoing emergency surgical revascularization, levosimendan in addition to standard catecholamines produced favorable effects.

Right Ventricular Dysfunction: Because levosimendan decreased PCWP more effectively than dobutamine, the substance may be of value in patients with reversibly increased pulmonary pressures or right ventricular dysfunction, *e.g.*, in patients during and after heart transplantation. Using dynamic positive emission tomography, pulmonary artery catheterization, and echocardiography, improved right ventricular mechanical efficiency (24%) was demonstrated after administration of an 18-micg/kg bolus and a 0.3-micg kg1 min1 continuous infusion of levosimendan in eight patients with NYHA functional class III or IV symptoms of heart failure in a double-blinded, crossover, placebo-controlled study.Although clinical data are sparse, administration of levosimendan with positive inotropic effects and parallel decreases in pulmonary pressures is promising in the setting of right ventricular dysfunction and could confirm the encouraging results of animal studies in this setting.

Combination with Other Positive Inotropic Drugs: Numerous reports of the efficacy of levosimendan as add-on therapy to catecholamines exist regarding improvement improvement in hemodynamic parameters clinical data evaluating specific combinations at specific doses, however, are lacking. Efficacy of addition of levosimendan (6-micg/kg bolus plus 0.2-micg kg1 min1 continuous infusion for 24 h) was shown in patients with NYHA functional class IV heart failure refractory to a continuous infusion of dobutamine (10 micg kg1 min1) and furosemide. In this study, combination of these positive inotropic drugs improved hemodynamics (increase in cardiac index 1.19 0.66 l min1 m2 and decrease in PCWP 5.4 8.7 mmHg) and consistently alleviated symptoms

than when compared with dobutamine alone (increase in cardiac index 0.44 0.32 l min1 m2 and increase in PCWP 1.0 4.4 mmHg) after 24 h. This investigation confirmed an experimental study in conscious dogs that demonstrated superiority of a combination therapy of dopamine and levosimendan (*i.e.*, levosimendan potentiated the positive inotropic effects of dopamine while attenuating its deleterious action on chamber compliance) over treatment with dopamine alone. Furthermore, addition of levosimendan to epinephrine during profound acidosis improved the attenuated efficacy of epinephrine in guinea pig hearts.

Other Possible Indications: Efficacy and safety of intermittent, long-term, concomitant dobutamine and levosimendan infusions in severe heart failure refractory to dobutamine alone were evaluated in 36 patients in NYHA functional class IV who were resistant to a 24-h continuous infusion of dobutamine in an uncontrolled, nonrandomized trial. The 45- day survival rates were 6% and 61% in patients treated with weekly dobutamine infusions and biweekly levosimendan infusions, respectively. Data regarding the use of levosimendan in children, pregnancy, and circulatory failure due to septic shock are rare, but published experience gives an encouraging view beyond the treatment of acutely decompensated CHF.

Economics: Currently, the clinically recommended administration of levosimendan is a single 24-h infusion, which is usually performed using one 12.5-mg vial with an average cost of approximately €700 ($875). A cost-effectiveness analysis was performed for intravenous treatment with levosimendan compared with dobutamine in patients with severe low-output heart failure based on the data of the LIDO study. Costs were based on study drug usage and hospitalization in the 6-month follow-up of the study, and the primary effectiveness measure was the gain in life expectancy. The mean survival in the LIDO study over 6 months was extrapolated (52 and 64 days for levosimendan- and dobutamine-treated patients, respectively). This assumed a mean additional lifetime of 3 yr based on the CONSENSUS trial due to the similar patient population, and the gain in life expectancy was estimated 0.35 yr/patient. Levosimendan increased the mean cost per patient by €1,108, which was attributable to the cost of the drug. Although the absolute difference in drug costs was relatively high (€1,024 *vs.* €41 for one treatment of levosimendan *vs.* dobutamine), the incremental cost per life-year saved was only €3,205 on European average, which is well below the acceptable threshold for cardiology therapies. Although the patients in the levosimendan group were alive for more days and thus risk for a longer period of hospitalization, there was no increase in resource utilization with levosimendan treatment compared with dobutamine.

Conclusion

Levosimendan is a positive inotropic drug with vasodilatingproperties that has been extensively investigated in experimental studies and that is also increasingly the subject of clinical trials. Clinical trials that are currently under way in the United States (REVIVE study) and Europe (SURVIVE study) aim to establish the role of levosi-mendan in short- and long-term therapy of patients with CHF. To date, clinical experience with levosimendan is encouraging because it combines several beneficial actions that considerably differ from other cardiotonic drugs. First, levosimendan enhances myocardial force without increasing intracellular Ca2 concentrations, which, in context with neutral effects on myocardial oxygen demand and heart rhythm, should be of benefit compared with catecholamines or PDE III inhibitors. Second, levosimendan does not impair myocardial relaxation, a possible limitation of other Ca2 sensitizers. Third, stimulation of ATP-sensitive potassium channels improves coronary blood flow, reduces preload and afterload, and may exert anti-ischemic actions. Finally, the drug has advantages on short- and long-term survival compared with standard inotropes and is safe, with low incidence of adverse effects when used in appropriate concentrations. Therefore, part of the benefit of levosimendan may also be achieved because it allows other inotropic agents that may have adverse effects on clinical outcome to be reduced in dose or avoided.

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