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Levosimendan, a New Inotropic and Vasodilator Agent

Wolfgang G. Toller, M.D., Christian Stranz, M.D.†*

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Several clinical studies suggest substantial limitations of currently available positive inotropic substances, including β_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 Ca^{2+} with subsequent increases in myocardial oxygen demand and arrhythmogenesis. Levosimendan, a myofilament Ca^{2+} 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. 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.[1] With the exception of digoxin, which has neutral effects on overall mortality,[2] currently available positive inotropic substances, including β_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.[3,4] 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,[5] particularly when concomitant ischemia is present as in patients with ischemic cardiomyopathy.[6] 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 (β_1-adrenoceptor agonists) or by a decreased rate of degradation (PDE III inhibitors), which promotes the release of Ca^{2+} from the sarcoplasmic reticulum (SR) to the cytosol. Augmentation of intracellular Ca^{2+} subsequently produces a temporary improvement in contractility at the expense of an increased myocardial energy consumption and oxygen demand,[7] which finally accelerates myocardial cell death. Furthermore, increased concentrations of cAMP and the subsequent change in intracellular Ca^{2+} turnover are cardiotoxic and enhance electrophysiologic mechanisms that result in rhythm disturbances.[8]

Accordingly, considerable research has been devoted to develop new approaches to positive inotropic therapy independent of the potentially deleterious mechanism of augmenting intracellular Ca^{2+} availability. Theoretically, such approaches should enhance contractile force without increasing myocardial oxygen demand or the risk of cardiac arrhythmias. As the relation of intracellular Ca^{2+} 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 Ca^{2+} levels.[9] All of these "myofilament Ca^{2+} 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.[10] Among these, levosimendan is promising in the management of both

* Associate Professor of Anesthesiology, † Resident.

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Address correspondence to Dr. Toller: Department of Anesthesiology and Intensive Care Medicine, Medical University Graz, Auenbruggerplatz 29, 8036 Graz, Austria. wolfgang.toller@meduni-graz.at. Individual article reprints may be accessed at no charge through the Journal Web site, www.anesthesiology.org.

acute and chronic left ventricular (LV) failure, because it is a potent Ca^{2+} sensitizer,[10] has no negative impact on diastolic function,[11] has little potency for additional PDE inhibition at clinically recommended concentrations,[12] has neutral effects on heart rhythm,[13] and has advantages over dobutamine in long-term survival.[14] 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[15] 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,[16] which is superior to catecholamines or PDE III inhibitors for this indication.

This review compares the different actions of standard positive inotropic drugs and Ca^{2+} 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 Ca^{2+} enters the cell, primarily through sarcolemmal voltage-gated L-type Ca^{2+} channels. This action on its own is insufficient to produce contraction of the myofilaments but triggers the (passive) release of larger amounts of Ca^{2+} from the SR to the cytosol ("calcium-induced Ca^{2+} release"),[17] 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 Ca^{2+} is low during relaxation (approximately 10^{-7} M), tropomyosin inhibits interaction between actin and myosin. Contraction is initiated when cytosolic Ca^{2+} increases (approximately 10^{-5} M), 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 Ca^{2+} is bound to TnC, this energy-dependent process is repeatedly performed ("cross-bridge cycling") to generate contractile force. During basal states, Ca^{2+} 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 Ca^{2+} available for binding or the sensitivity of myofilaments to Ca^{2+}. Relaxation is initiated both by phosphorylation of TnI and rapid removal of cytosolic Ca^{2+} 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 Ca^{2+}.

Importantly, the response of myofilaments to a specific intracellular concentration of Ca^{2+} may be attenuated (*i.e.*, "desensitization") by a variety of pathophysiologic conditions, including acidosis,[18] hypothermia,[19,20] increased inorganic phosphate,[21] sepsis,[22] ischemia–reperfusion injury,[23] and myocardial stunning,[24] but also by pharmacologic β-adrenergic stimulation[25–27] or the presence of CHF with increased neurohormonal activation. Conversely, the sensitivity of contractile proteins to Ca^{2+} may increase, *e.g.*, by α-adrenergic receptor stimulation[27] or by administration of myofilament calcium sensitizers.[10]

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 Ca^{2+} concentration (fig. 1). Binding of catecholamines to β_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 L-type Ca^{2+} channel, phospholamban, and TnI. Phosphorylation of sarcolemmal voltage-gated L-type Ca^{2+} channels enhances Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} availability from the SR for the next cellular depolarization and contributes to the overall gain in cardiac excitation–contraction coupling that adrenergic stimulation medi-

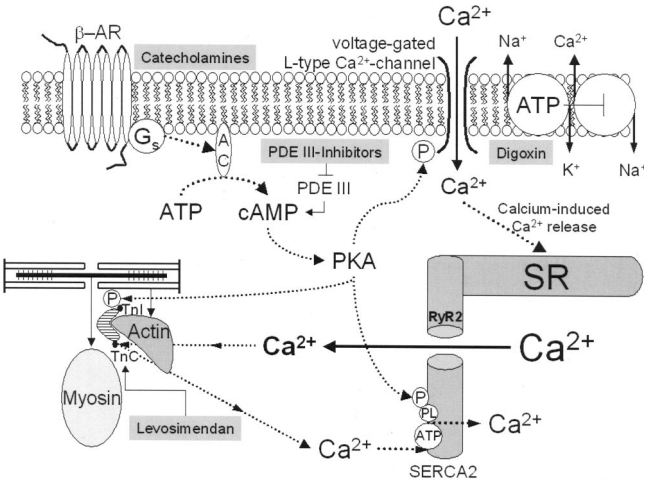

Fig. 1. Schematic illustration mechanism of action of positive inotropic drugs. β-Adrenergic stimulation (catecholamines) and phosphodiesterase (PDE) III inhibition increase cyclic adenosine monophosphate (cAMP), which acts *via* protein kinase A (PKA) to phosphorylate calcium channel protein, phospholamban (PL), and troponin I (TnI). Phosphorylation (P) of calcium channel protein enhances sarcolemmal inward movement of Ca^{2+}, which subsequently increases Ca^{2+} movement from the sarcoplasmic reticulum (SR) through the calcium release channel (ryanodine receptor type 2 [RyR2]) to the cytosol (calcium-induced Ca^{2+} release). Digoxin increases cytosolic Ca^{2+} by inhibition of sarcolemmal Na^+–K^+–adenosine triphosphatase and Na^+–Ca^{2+} exchange. Cytosolic Ca^{2+} binds to troponin C (TnC) and initiates contraction (inotropic effect). Phosphorylation of PL enhances relaxation by increased reuptake of Ca^{2+} back into the SR by the SR Ca^{2+} adenosine triphosphatase isoform 2 (SERCA2) (lusitropic effect). Phosphorylation of TnI enhances the rate of relaxation by decreasing the sensitivity of myofilaments to Ca^{2+}. Levosimendan binds to TnC during systole and thereby increases the sensitivity of myofilaments to Ca^{2+} without alteration of Ca^{2+} levels. AC = adenylate cyclase; ATP = adenosine triphosphate; β-AR = β adrenoceptor; G_s = stimulatory guanine nucleotide binding proteins.

ates. The consequences of this increased loading of the SR with Ca^{2+} may be a key factor in the development of Ca^{2+}-mediated arrhythmias.[8] Phosphorylation of TnI decreases the affinity of myofilaments for Ca^{2+} and thereby also favors relaxation.[28–30] Together, these effects provide an integrated response to β-adrenergic stimulation that increases myocardial contractility, while in parallel supports myocardial relaxation by desensitizing myofilaments and augmenting the active removal of Ca^{2+} 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 Ca^{2+} from the cytosol into the extracellular compartment by the Na^+–Ca^{2+} exchanger. Ca^{2+} not extruded from the cytosol by this mechanism is stored in the SR and allows increased release of Ca^{2+} 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.[31]

Mechanism of Action of Levosimendan

Positive Inotropic Effects

Myofilament Ca^{2+} Sensitization. Levosimendan enhances myocardial contractility by binding to the N-terminal lobe of cardiac TnC with a high affinity[32–34] and stabilizing the Ca^{2+}-bound conformation of this regulatory protein.[32] Therefore, systolic interaction of actin-myosin filaments is prolonged without alteration of the rate of cross-bridge cycling. Other myofilament Ca^{2+} sensitizers are bound to the TnC–Ca^{2+} complex during both systole and diastole with improvement of systolic but possible impairment of diastolic function[35] due to facilitation of cross-bridging at diastolic Ca^{2+} levels, whereas binding of levosimendan to TnC is dependent on the cytosolic Ca^{2+} concentration, *i.e.*, increases during systole but is relatively unchanged during diastole, when Ca^{2+} levels decrease.[36] 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[36–38] and clinical[11,39] studies.

Phosphodiesterase III Inhibition. In addition to myofilament Ca^{2+} sensitization, levosimendan inhibits cardiac PDE, predominately PDE III,[40] in muscle strips from human hearts[41] and various animal models.[12,40,42] This effect is observed predominately at higher concentrations (> 0.3 μM),[12,43] but is not seen (0.03 μM) or is less pronounced (0.1–0.3 μM) at concentrations reflecting the clinically recommended therapeutic range of 0.03–0.3 μM (*i.e.*, 10–100 ng/ml).[44,45] Therefore, at concentrations of 0.03–0.1 μM, levosimendan does not alter heart rate, cAMP levels, myocardial relaxation,[12] and cytosolic Ca^{2+} as assessed by aequorin light transients,[37,41] although it significantly increases myocardial contractility in guinea pig hearts[12] and shifts the graph of the relation between Ca^{2+} and contractile force to the left.[37] These findings indicate that levosimendan mainly acts as a Ca^{2+} sensitizer at concentrations of 0.03–0.1 μM. Although 0.1–0.3 μM levosimendan variably alters myocardial cAMP levels, heart rate, ^{32}P incorporation into phospholamban,[12] and aequorin light transients,[41] concentrations exceeding 0.3 μM consistently increase heart rate, contraction (+dP/dt) and relaxation (−dP/dt) as well as partial phosphorylation of phospholamban[12] and aequorin light transients.[41] These findings suggest a contributing role of PDE inhibition at concentrations of levosimendan exceeding 0.3 μM.

Important experimental and clinical differences between levosimendan and classic PDE inhibitors (*e.g.*,

milrinone), however, exist. First, milrinone has no Ca^{2+} sensitizing effect,[46] but in contrast decreases the sensitivity of myofilaments to Ca^{2+} through cAMP-dependent phosphorylation of TnI, whereas levosimendan has this action.[12] Second, milrinone consistently exerts positive inotropic effects in parallel with an increase in aequorin light emission (indicating influence on Ca^{2+} transients),[41] whereas levosimendan at low concentrations does not have this effect despite production of positive inotropic effects, suggesting that levosimendan is more potent as a Ca^{2+} sensitizer than as an inhibitor of PDE.[12,47] Third, metabolism of levosimendan produces a long-lasting active metabolite, OR-1896,[48] which has similar Ca^{2+} sensitizing properties like the parent compound[49] but a significantly lower potential to inhibit PDE III (40-fold less potent, 3-fold less selective).[40] 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[50] suggest an important role of Ca^{2+} sensitization of this metabolite. Fourth, in clinical practice, levosimendan does not increase the incidence of arrhythmias,[13] worsen ischemia,[51] or negatively influence patient outcome,[14,51] whereas milrinone does.[4–6]

Vasodilation

Levosimendan produces vasodilation in several vasculatures including coronary,[52–54] pulmonary,[55] renal,[56] splanchnic,[56] cerebral,[56] and systemic[57,58] arteries as well as saphenous,[59] portal,[60] and systemic[57,58] veins. The underlying mechanism of vasodilation has been extensively investigated[54,55] 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,[53,61] and pulmonary[55] arteries is opening of potassium channels, including ATP-sensitive K^+ (K_{ATP}) channels in small resistance vessels and Ca^{2+}-activated K^+ and voltage-dependent K^+ channels in large conductance vessels.[62,63] Opening of these channels hyperpolarizes the membrane, inhibits inward Ca^{2+} current, and activates the Na^+–Ca^{2+} exchanger to extrude Ca^{2+}. The resultant decrease in intracellular Ca^{2+} produces vasorelaxation. Attenuation of levosimendan-induced dilation of coronary arteries during concomitant administration of the K_{ATP} channel antagonist glibenclamide emphasizes the role of K_{ATP} channels in this setting.[53,61]

A second mechanism involved in levosimendan-induced vasodilation is reduction of Ca^{2+} sensitivity of the (TnC-lacking) contractile proteins in vascular smooth muscle.[64] This decrease in contractile force of vascular myofilaments occurs without a proportionate decrease in intracellular Ca^{2+}. In addition, PDE inhibition has been proposed to contribute to levosimendan-induced vasodilation because of increases in cAMP in vascular

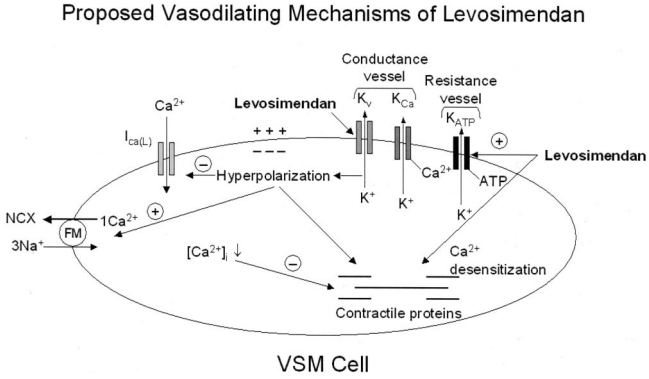

Fig. 2. Proposed vasodilating mechanisms for levosimendan. Levosimendan stimulates the adenosine triphosphate (ATP)–sensitive K^+ (K_{ATP}) channel in small resistance vessels and the Ca^{2+}-activated K^+ (K_{Ca}) and voltage-dependent K^+ (K_V) channels in large conductance vessels. These actions hyperpolarize the membrane, thereby inhibiting inward L-type Ca^{2+} current ($I_{Ca(L)}$), as well as promoting the forward mode (FM) of Na^+–Ca^{2+} exchanger (NCX), *i.e.*, three Na^+ in, one Ca^{2+} out. The resultant decrease in intracellular Ca^{2+} ($[Ca^{2+}]_i$) would produce vasorelaxation. Levosimendan also may decrease the Ca^{2+} 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. Modified from figure 1, with kind permission of Springer Science and Business Media, from Yokoshiki and Sperelakis.[63]

smooth muscle.[65] This effect, however, predominately occurs at excessive doses (1 mM) of levosimendan,[54] whereas at 3 μM, vasorelaxation is different from milrinone[64] and not affected by inhibition of protein kinase A at concentrations of 0.01–1 μM.[47] 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.

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 ($\geq$ 0.1 μM) increased heart rate in several animal experiments,[12,38,42] healthy volunteers,[66] and patients with New York Heart Association (NYHA) functional class II–IV heart failure of ischemic etiology.[45] 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,[67] particularly after administration of a bolus. Conversely, studies demonstrate an initial neutral effect on heart rate after abandonment of a bolus,[68] low bolus

concentrations (3–12 μg/kg),[51,66,69] or oral administration of levosimendan.[70] In contrast, persistence of an increased heart rate after discontinuation of a 24-h infusion of levosimendan[48,50] or after extended infusions for 7 days[71] suggests an important role of OR-1896, a metabolite of levosimendan,[48] which continues to accumulate after withdrawal of levosimendan.[50] In clinical practice, treatment of patients with normal or reduced ejection fraction but within the recommended dosages (6- to 24-μg/kg bolus over 10-min, followed by an infusion of 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$)[45] rarely produces positive chronotropy exceeding more than 10% from baseline[45] 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,[45] cardiogenic shock,[72] and severe decompensated low-output heart failure[14,58,73] and after myocardial infarction,[51] but also in the perioperative period in patients undergoing surgical revascularization with normal[39] or compromised[74] ventricular function. In contrast, administration of high doses of levosimendan (36-μg/kg bolus and infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 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.[75] Therefore, changes in heart rate are obviously a function of dosage, intravascular volume status, and preexisting compromise of myocardial contractile function.[76] Taken together, modification of heart rate under clinical conditions and within the recommended doses[45] is unlikely to be an important mechanism of the increase in cardiac output produced by levosimendan.

Cardiac Performance

Administration of levosimendan enhances cardiac performance *in vitro*,[41] *in vivo*,[76] and in clinical studies.[14,58] For example, in patients with low-output heart failure, a 24-h administration of levosimendan (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increased cardiac output by 1.09 l/min and decreased pulmonary capillary wedge pressure (PCWP) by 7 mmHg, whereas dobutamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) changed these parameters by 0.80 l/min and 3 mmHg, respectively (fig. 3).[14] 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.[58] 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 (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in patients with decompensated CHF and a mean LV ejection fraction of approximately 25%.[77] Interestingly, the decrease of this neurohormonal marker was particularly pronounced 48 h after discontinuation of levosimendan treatment.

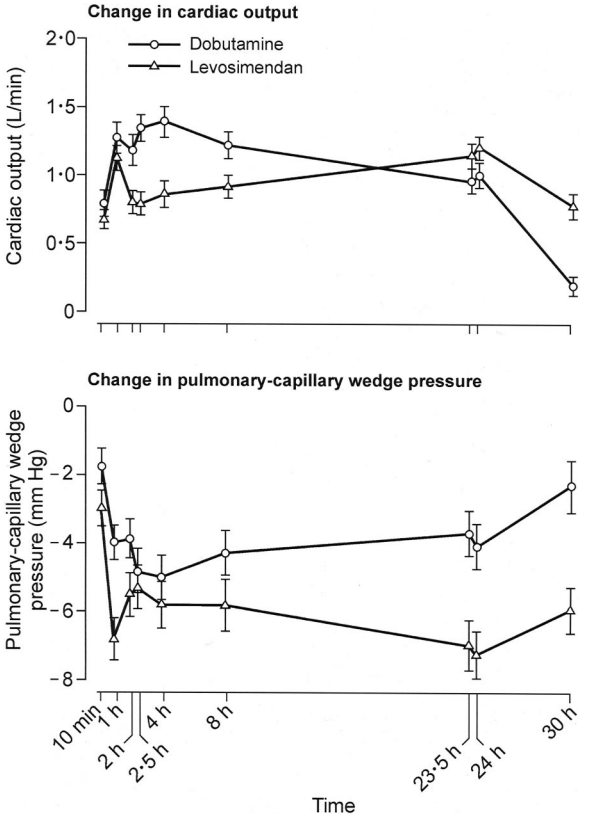

Fig. 3. Comparison of hemodynamic effects of levosimendan and dobutamine. Changes in cardiac output and pulmonary capillary wedge pressure were recorded from baseline to 30 h in patients with low-output heart failure. Levosimendan (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or dobutamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) 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. Reprinted with permission from Elsevier, from Follath *et al.*[14]

Although Ca^{2+} sensitizers carry a potential risk of worsening diastolic function,[35] levosimendan decreased the time constant of isovolumic relaxation (τ) in various experimental[38,76,78] and clinical[11] 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.[79] These positive lusitropic effects may be related to the Ca^{2+} dependence of Ca^{2+}-bound sensitization of cardiac TnC, *i.e.*, the contractile apparatus is sensitized in systole (when Ca^{2+} is high) but not in diastole (when Ca^{2+} is low) or alternatively due to PDE III inhibition.

Vasodilation

Vasodilation observed with administration of levosimendan is followed by numerous consequences. Pulmonary vasodilation decreases right heart filling pressures,[58] which, in context with positive inotropic

effects, could explain increases right ventricular contractility and performance observed with administration of levosimendan.[80,81] Systemic vasodilation decreases left heart filling pressures, enhances LV–arterial coupling,[57] and increases blood flow to various tissues, including myocardium, gastric mucosa,[82] renal medulla, small intestine, and liver.[56] In the splanchnic area, levosimendan is superior to milrinone and dobutamine in selectively increasing microvascular gastric mucosal oxygenation[82,83] and increases portal venous blood flow and oxygen delivery in experimental septic shock.[84] 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in patients with low-output heart failure as demonstrated by decreases of serum creatinine levels (−9 μM) compared with infusions of dobutamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[14]

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.[5,6,85,86] In this setting, availability of positive inotropic drugs with a neutral profile on cardiac rhythm and anti-ischemic effects would confer benefits.

K_{ATP} Channel Opening

Levosimendan opens both mitochondrial[87,88] and sarcolemmal[89,90] K_{ATP} channels. Although the definite relevance of these actions is unknown, opening of mitochondrial K_{ATP} channel has repeatedly been implicated in mediation of anti-ischemic actions.[91] Prevention of mitochondrial Ca^{2+} 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.[92] Interestingly, the positive inotrope levosimendan protected ischemic myocardium,[85,93] decreased myocardial infarct size when administered before and during myocardial ischemia in dogs,[61] and improved survival compared with placebo in patients with LV failure complicating acute myocardial infarction.[51]

Opening of sarcolemmal K_{ATP} channels, however, has been implicated in both mediating cardioprotective effects[94] and exerting a theoretical proarrhythmic potential.[95] This detrimental action on heart rhythm is produced by the large outward repolarizing K^+ current that sarcolemmal K_{ATP} channel opening initiates. Subsequent hyperpolarization of resting membrane potential and shortening of action potential duration decreases the effective refractory period[96] of the tissue and thereby increases the susceptibility to reentrant arrhythmias. Although levosimendan indeed hyperpolarized membrane potential,[89] shortened action potential duration in isolated cells,[90] and slightly shortened effective refractory period in patients,[97] experimental and clinical studies so far have demonstrated a neutral effect of this drug on heart rhythm rather than proarrhythmic potential.[13,85,97]

Effects of Levosimendan during Ischemia, Stunning, and Myocardial Infarction

Because levosimendan does not increase myocardial oxygen demand[81] and possibly exerts anti-ischemic effects,[61,93,98] 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[85] and in patients with stable moderate-to-severe ischemic cardiomyopathy when used in recommended clinical concentrations (6- to 24-μg/kg bolus over 10 min, followed by an infusion of 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in a double-blinded, placebo-controlled, randomized, multicenter study.[45] Furthermore, the incidence of arrhythmias was not increased when levosimendan was compared with placebo in patients with acute myocardial infarction[51] or administered perioperatively in patients with coronary artery bypass grafting.[75] Although obviously having a neutral profile on heart rhythm, levosimendan consistently improved contractile function in the setting of global ischemia–reperfusion injury in experimental[85,93,99,100] and clinical studies.[11,51,75]

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[101] and worsening of the myocardial contractile function in the ischemic area.[102] An increased frequency of ventricular arrhythmias was also noted at levosimendan doses of 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (*i.e.*, 3 times higher than upper recommended dose) in patients with stable ischemic cardiomyopathy.[45] 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.[103] 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[104,105] and in patients with acute coronary syndrome undergoing angioplasty in a randomized, double-blinded, placebo-controlled trial.[11] Administra-

Table 1. Pharmacokinetics of Levosimendan in Healthy Volunteers and Patients with Congestive Heart Failure

	Healthy Volunteers		Patients with CHF	
	Unchanged Levosimendan	Total Drug	Unchanged Levosimendan	Total Drug
$t_{1/2\alpha}$, h	0.20 ± 0.08	0.16 ± 0.08	0.26 ± 0.08	0.17 ± 0.08
$t_{1/2\beta}$, hr	0.96 ± 0.16	0.92 ± 0.16	1.03 ± 0.11	0.94 ± 0.29
$t_{1/2\gamma}$, h	—	5.73 ± 1.53	—	5.23 ± 0.99
Cl_{tot}, ml/min	359 ± 69	104 ± 15	296 ± 61	85 ± 20
V_c, l	12.3 ± 3.3	7.6 ± 0.9	13.0 ± 2.7	7.3 ± 1.3
V_s, l	21.9 ± 5.9	27.9 ± 5.3	19.5 ± 4.5	23.8 ± 2.8
V_{area}, l	30.3 ± 9.1	52.2 ± 20.1	26.4 ± 5.9	37.4 ± 5.5

Data are mean ± SD; n = 15 for both groups.

CHF = congestive heart failure; Cl_{tot} = total clearance; $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ = α, β, and total elimination half-lives; V_{area} = volume of distribution based on area under the curve; V_c = central volume of distribution; V_s = volume of distribution at steady state.

Reprinted with permission from Lippincott Williams & Wilkins, Sandell *et al.*[108]

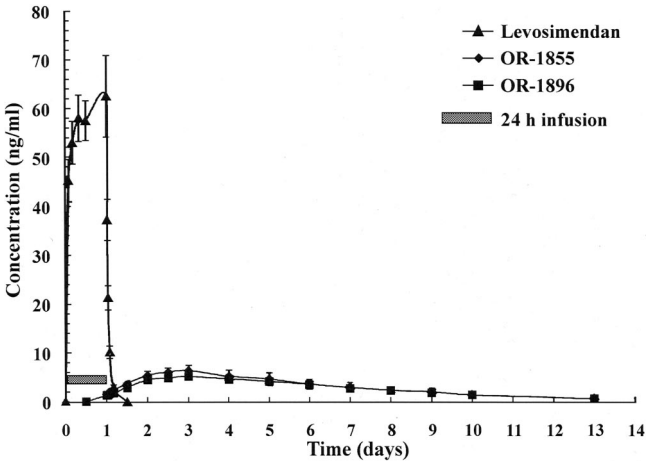

Fig. 4. Plasma concentrations of levosimendan and its metabolites, OR-1855 and OR-1896, during and after a 24-h infusion of levosimendan in patients with chronic heart failure. Concentrations of levosimendan decline quickly after discontinuation of the infusion, whereas both metabolites reach maximum plasma concentrations approximately 2 days after withdrawal of levosimendan. *Error bars* indicate SEMs. Reprinted with permission from Dustri-Verlag, Inc., from Kivikko *et al.*[48]

tion of levosimendan before or during myocardial stunning is of special interest not only because of the myofilament Ca^{2+} sensitization of this drug. The decrease in myofilament responsiveness that characterizes stunning can also be prevented by ischemic preconditioning.[24] Because opening of myocardial K_{ATP} channels plays a key role in the mediation of ischemic preconditioning, one may speculate that administration of the K_{ATP} channel opener levosimendan before ischemia may also prevent or attenuate the negative effects of myocardial stunning. Levosimendan also has cardioprotective effects by opening K_{ATP} 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.[61]

Pharmacokinetics, Metabolism, and Dosage

The pharmacologic profile of levosimendan and its metabolites in patients with normal and compromised myocardial contractile function has been reviewed extensively elsewhere.[106] Important pharmacokinetic data of levosimendan in healthy volunteers and patients with congestive heart failure are shown in table 1.

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,[107] pharmacokinetic parameters of intravenous levosimendan are comparable when obtained in healthy volunteers and patients with mild[108] or NYHA functional class III or IV heart failure.[44] Levosimendan has a β elimination half-life, volume of distribution, and total body clearance of approximately 1 h, 20 l, and 300 ml/min, respectively. These parameters remain constant independent of the duration of infusion.[71] 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.[108]

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 Ca^{2+}-sensitizing and weak PDE III–inhibiting properties[49] and exerts positive inotropic effects similar to the parent compound.[109] OR-1896, however, has an elimination half-life of 80–96 h,[48] reaches maximum plasma concentrations approximately 2 days after withdrawal of a 24-h infusion of levosimendan in patients with CHF (fig. 4), and is likely to be responsible for the sustained or greater hemodynamic effects observed after discontinuation of levosimendan.[48,50] 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.[50,71,110] Pharmacokinetics of levosimendan were similar after single-dose administration and continuous infusion of 7 days,[110] whereas accumulation of OR-1896 was confirmed.[71] An extended infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 7 days decreased systolic blood pressure (11 ± 14 mmHg) and substantially increased heart rate (26 ± 19 beats/min) on 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%.[71]

Dosage

Administration of a 6- to 24-μg/kg bolus dose of levosimendan followed by a 24-h infusion of 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produces plasma concentrations of 10–100 ng/ml (0.035–0.35 μM) in patients with NYHA functional class II–IV heart failure[44] and can be considered as the therapeutic range to obtain favorable hemodynamic effects.[45]

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%).[45,51,58]

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.[14,45,51,58] 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 β blockers.[14] Although additive responses particularly regarding vasodilation (*i.e.*, ACE inhibitors and levosimendan) and heart rate (*i.e.*, nitrates or β 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 β blockade on hemodynamics revealed no reduction of the effects of levosimendan on cardiac output and PCWP, whereas the actions of dobutamine were attenuated.[14] This finding is in agreement with previous preclinical and clinical data demonstrating beneficial or neutral effects of parallel atenolol[47] or carvedilol[111] 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.[45] Although no direct comparisons were made between patients with or without these drugs, treatment with levosimendan within the recommended doses (0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in general was associated with only minor decreases in mean arterial blood pressure (3.5 ± 2.8 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.[112] 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.[113] 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).[51] 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.[114] No exaggerated or attenuated hemodynamic side effects of levosimendan were further reported in the presence of furosemide (10 mg/h) and amiodarone.[73]

Hemodynamic Side Effects

Dose-dependent increases in heart rate and decreases in mean arterial blood pressure and total peripheral and pulmonary vascular resistance[45] 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[45,51] and symptomatic or asymptomatic hypotension (> 10-mmHg pressure decrease).[51] Levosimendan-induced vasodilation may, however, be responsible for the increased frequency of headache, dizziness, and nausea observed in several clinical trials.[14,45,113]

Electrophysiologic Side Effects

Short-term intravenous administration (18-μg/kg bolus followed by 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increases heart rate, shortens sinus node cycle duration and sinus node recovery time, and decreases atrioventricular nodal conduction interval and refractory periods.[115] 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,[45,48,51,71] 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 μg/kg over 10 min followed by an infusion of 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the QTc interval remained unaffected.[45] Single-bolus injections of 6.5 and 25 μg/kg without subsequent continuous infusion in healthy men produced QTc prolongations as assessed by the Bazett equation of +6 ms and +21 ms,

respectively.[116] In contrast, administration of bolus doses of 24 and 36 μg/kg followed by continuous infusions of 0.4 and 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ prolonged QTc duration by 15 ± 20 and 45 ± 10 ms in patients with NYHA functional class II–IV heart failure.[45] Continuous infusions of levosimendan in doses of 0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but over 7 days increased mean QTc values by 38 ± 42 and 52 ± 40 ms.[71]

The impact of this proarrhythmic potential of levosimendan must be weighed against possible antiarrhythmic actions due to the lack of cytosolic Ca^{2+} 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.[13]

Other Side Effects

Serum potassium levels,[45] erythrocyte count, and hemoglobin and hematocrit values may slightly decrease after prolonged levosimendan infusion,[71] 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.[14] These patients had an LV ejection fraction of less than 35%, a cardiac index of less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$, 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. A bolus of levosimendan of 24 μg/kg was infused over 10 min, followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 24 h. Dobutamine was infused for 24 h at an initial dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without a bolus. The infusion rate of each drug was doubled (*i.e.*, 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ levosimendan and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 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% or more) at 24 h. All-cause mortality was assessed prospectively at 31 days and retrospectively at 180 days after randomization. Levosimendan treatment was superior to dobutamine in increasing cardiac output and decreasing PCWP (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 β-blocker therapy, whereas the actions of dobutamine 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.

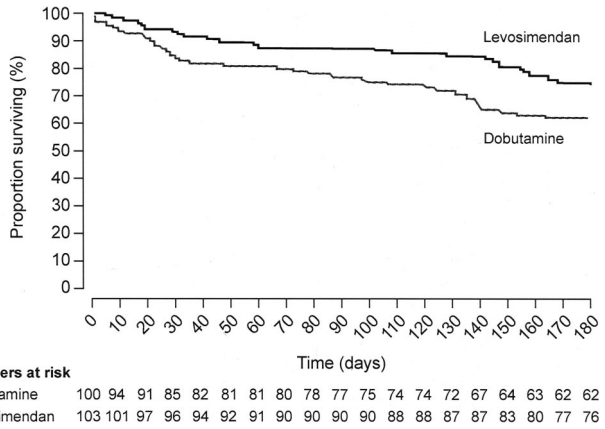

Fig. 5. Kaplan-Meier estimates of risk of death during 180 days after a 24-h infusion of levosimendan (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or dobutamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in patients with low-output heart failure. Administration of levosimendan was associated with both a significantly lower 31-day (8% *vs.* 17%; $P = 0.045$) and 180-day (26% *vs.* 38%; $P = 0.029$) mortality. Reprinted with permission from Elsevier, from Follath *et al.*[14]

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.[58] In these patients with NYHA func-

tional 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 μg/kg, followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At hourly intervals, a repeat bolus of 6 μg/kg was given, and the infusion rate was up-titrated by increments of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until a maximum rate of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 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 $\leq$ 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 $\pm$ 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.[51] In this investigation, four different dosing regimens of levosimendan were tested (6- to 24-μg/kg bolus infused over a period of 10 min, followed by 6 h infusions of 0.1–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$). At the time of levosimendan administration, most patients were using nitrates and diuretics, approximately 40% were using ACE inhibitors or β 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 (24-μg/kg bolus followed by 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$), a trend toward higher frequency of ischemia and hypotension was observed, but these effects were not evident at lower doses (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 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,[14] did not aggravate ischemia in patients with stable coronary heart disease as assessed by a 24-h Holter electrocardiogram,[114] and enhanced cardiac output in patients with ischemic heart disease and LV dysfunction,[69] 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[101,102] 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.[103]

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.[11] Levosimendan (24 μg/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 $\pm$ 0.9 to 6.5 $\pm$ 1.1 when compared with placebo (7.8 $\pm$ 1.0 to 8.5 $\pm$ 1.1). This action occurred 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.[14,74,117] In a randomized, double-blinded, placebo-controlled study, levosimendan (18- or 36-μg/kg bolus and 0.2- or 0.3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ 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.[75] In this study, administration of the 36-μg/kg bolus instantly increased heart rate, although this effect vanished after 1 h despite continuation of the infusion. Similarly, levosimendan (8 or 24 μg/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%.[39] 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 μg/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.[118]

Cardiogenic Shock

In the presence of refractory cardiogenic shock (defined as cardiac index $< 2.2\ l \cdot min^{-1} \cdot m^{-2}$, PCWP >16 mmHg, systolic blood pressure < 90 mmHg, and requirement of catecholamines), 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ levosimendan for 24 h as add-on therapy favorably altered hemodynamic parameters by increasing cardiac index from 1.8 ± 0.4 to 2.4 ± 0.6 $l \cdot min^{-1} \cdot m^{-2}$ and decreasing systemic vascular resistance from 1,559 ± 430 dyn · s · cm^{-5} to 1,109 ± 202 dyn · s · cm^{-5}, 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.[72] Similarly, in a case series of 10 patients with cardiogenic shock undergoing emergency surgical revascularization, levosimendan in addition to standard catecholamines produced favorable effects.[74]

Right Ventricular Dysfunction

Because levosimendan decreased PCWP more effectively than dobutamine,[14] 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-μg/kg bolus and a 0.3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ 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.[81] 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[119] and could confirm the encouraging results of animal studies[80] 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 in hemodynamic parameters[68,72,74,117,120,121]; clinical data evaluating specific combinations at specific doses, however, are lacking. Efficacy of addition of levosimendan (6-μg/kg bolus plus 0.2-$\mu g \cdot kg^{-1} \cdot min^{-1}$ continuous infusion for 24 h) was shown in patients with NYHA functional class IV heart failure refractory to a continuous infusion of dobutamine (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and furosemide.[73] In this study, combination of these positive inotropic drugs improved hemodynamics (increase in cardiac index 1.19 ± 0.66 $l \cdot min^{-1} \cdot m^{-2}$ 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 $l \cdot min^{-1} \cdot m^{-2}$ 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.[122] Furthermore, addition of levosimendan to epinephrine during profound acidosis improved the attenuated efficacy of epinephrine in guinea pig hearts.[123]

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.[124]

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.[80,82–84,121,125–127]

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.[128] 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 (157 ± 52 and 139 ± 64 days for levosi-

mendan- and dobutamine-treated patients, respectively). This assumed a mean additional lifetime of 3 yr based on the CONSENSUS trial[129] due to the similar patient population, and the gain in life expectancy was estimated at 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 at 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 vasodilating properties 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 in Europe (SURVIVE study) aim to establish the role of levosimendan 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 Ca^{2+} 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 Ca^{2+} 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 a 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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