Levosimendan: Beyond its simple inotropic effect in heart failure

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Abstract

Classic inotropic agents provide short-term haemodynamic improvement in patients with heart failure, but their use has been associated with poor prognosis. A new category of inotropic agents, the Ca²⁺ sensitizers, may provide an alternative longer lasting solution. Levosimendan is a relatively new Ca²⁺ sensitizer which offers haemodynamic and symptomatic improvement by combining a positive inotropic action via Ca²⁺ sensitization and a vasodilatory effect via adenosine triphosphate(ATP)-sensitive K⁺ (K_ATP), Ca²⁺-activated K⁺ (K_Ca²⁺) and voltage-dependent K⁺ (K_V) channels activation. Levosimendan also seems to induce a prolonged haemodynamic improvement in patients with heart failure as a result of the long half-life of its active metabolite, OR-1896. Furthermore, there is also evidence that levosimendan may have additional antiinflammatory and antiapoptotic properties, affecting important pathways in the pathophysiology of heart failure. Despite the initial reports for a clear benefit of levosimendan on short- and long-term mortality in patients with severe heart failure, the results from the recent clinical trials are rather disappointing, and it is still unclear whether it is superior to dobutamine in affecting survival of patients with severe heart failure. In conclusion, levosimendan is a promising agent for the treatment of decompensated heart failure. As further to its positive inotropic effect, it affects multiple pathways with key roles in the pathophysiology of heart failure. The results of the ongoing trials examining the effect of levosimendan on mortality in patients with heart failure will hopefully resolve the controversy as to whether levosimendan is superior to classic inotropic agents for the treatment of severe heart failure.

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Keywords: Levosimendan; Heart failure; Ca²⁺ sensitizers; Myocardial function

Abbreviations: ace, angiotensin-converting enzyme inhibitor; BNP, NT-pro-brain natriuretic peptide; CASINO, calcium sensitizer or inotrope or none in low output heart failure study; CHF, congestive heart failure; K_ATP, ATP-sensitive K⁺ channels; K_Ca²⁺, Ca²⁺-activated K⁺ channels; K_V, voltage-dependent K⁺ channels; LIDO, levosimendan infusion versus dobutamine in severe low output heart failure study; NYHA, New York Heart Association functional class; NF-κB, nuclear factor kappa B; PCWP, pulmonary capillary wedge pressure; PDE, phosphodiesterase; REVIVE, randomized multicenter evaluation of intravenous levosimendan efficacy versus placebo in the short-term treatment of decompensated heart failure; RUSSLAN, randomised study on safety and effectiveness of levosimendan in patients with left ventricular failure after an acute myocardial infarct; sFAS, soluble FAS; SURVIVE, survival of patients with acute heart failure in need of intravenous inotropic support study.

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1. Introduction

Heart failure is characterised by decreased cardiac output, resulting in both pulmonary congestion and peripheral hypoperfusion; it is accompanied by neurovascular activation, enhancement of systemic inflammatory process and cachexia (Thackray et al., 2001). The currently used combined therapy for heart failure [with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists and high-dose loop diuretics] offers symptomatic relief and improves the short-term prognosis of patients with heart failure. Although the currently used inotropic agents seem to be useful for the short-term treatment of acute heart failure, evidence suggests that their use is associated with increased mortality and several side effects (Thackray et al., 2001). As a general principle, the classic inotropic agents operate through the adrenergic nervous signaling pathway, the sodium–potassium pump, or the inhibition of phosphodiesterase (PDE), leading to the increase of intracellular Ca\(^{2+}\) levels (Thackray et al., 2001), but they can induce dangerous arrhythmias (Majerus et al., 1989). Ca\(^{2+}\) sensitizers, a relatively new category of inotropic agents, exert their inotropic action by increasing the sensitivity of the myocardial contractile system to intracellular Ca\(^{2+}\) (Ukkonen et al., 2006). The most commonly used agent of this category, the class III Ca\(^{2+}\) sensitizer levosimendan, offers symptomatic relief and improves the short-term prognosis of patients with heart failure. Although the currently used inotropic agents seem to be useful for the short-term treatment of acute heart failure, evidence suggests that their use is associated with increased mortality and several side effects (Thackray et al., 2001). As a general principle, the classic inotropic agents operate through the adrenergic nervous signaling pathway, the sodium–potassium pump, or the inhibition of phosphodiesterase (PDE), leading to the increase of intracellular Ca\(^{2+}\) levels (Thackray et al., 2001), but they can induce dangerous arrhythmias (Majerus et al., 1989). Ca\(^{2+}\) sensitizers, a relatively new category of inotropic agents, exert their inotropic action by increasing the sensitivity of the myocardial contractile system to intracellular Ca\(^{2+}\) (Ukkonen et al., 2000; Koumallos et al., 2006). The most commonly used agent of this category, the class III Ca\(^{2+}\) sensitizer levosimendan, seems to offer new therapeutic opportunities to patients with heart failure, since, further to the simple inotropic effect, it has a number of additional beneficial effect in heart failure patients by acting as a vasodilator in resistance vessels and modifying critical pathways implicated in the pathophysiology of heart failure.

2. Pharmacokinetics and metabolism of levosimendan

Levosimendan has high oral bioavailability, but in clinical practice it has only been developed for intravenous administration. Steady state is achieved within 5 hr of a constant dose infusion. It has an elimination half-life of ∼1 hr and body clearance ∼300 mL/min (Haikala & Linden, 1995; Sandell et al., 1995; Antila et al., 1999; Kivikko et al., 2002a,b). Only a small proportion (∼4%) of the drug is free in plasma, since >90% is bound to albumin. After infusion, levosimendan is acetylated to form 2 biologically active metabolites, OR-1896 and OR-1855, with much longer elimination half-lives (Kivikko et al., 2002a,b; Antila et al., 2004) than levosimendan itself, while their pharmacologic effects persist for ∼1 week. OR-1855, an intermediate metabolite in the conversion of levosimendan to OR-1896, is formed by the acetylation of levosimendan by intestinal bacteria, and is excreted by the biliary route. Approximately 40% of these metabolites are also bound to plasma proteins, while they are eliminated in urine and feces.

The most clinically relevant metabolite is OR-1896, which has similar pharmacodynamic properties as the parent drug (Kristof et al., 1998). This metabolite has an elimination half-life ∼80 hr, whereas for 24-hr infusions it reaches its maximum concentrations 2 days after the end of infusion (Kivikko et al., 2002a,b). Therefore, this metabolite is probably responsible for the prolonged haemodynamic effects of levosimendan, which seem to persist for many days after infusion (Kivikko et al., 2002a,b). This long half-life of OR-1896 seems to lead to its accumulation after prolonged infusions, exceeding 24 hr (Kivikko et al., 2002a,b). Although prolonged infusion of levosimendan (up to 1 week at a dosage of 0.1 μg/kg/min) may lead to accumulation of OR-1896, it does not seem to have any dangerous side effects (Kivikko et al., 2002a,b). However, the recommended dosage for levosimendan has been set to an initial 6–24 μg/kg of bolus administration followed by a 24-hr infusion of 0.05–0.2 μg/kg/min (Toller & Stranz, 2006). This leads to the optimum haemodynamic effects (Nieminen et al., 2000). Pharmacokinetic studies have demonstrated that 24-hr levosimendan infusion (0.2 μg/kg/min) achieves maximal free (nonprotein bound) plasma concentrations 6 nM for levosimendan and 12 nM for OR-1896 (Kivikko et al., 2002a,b). These concentrations are of major importance, since the pharmacologic effects of these 2 molecules are largely dependent on the achieved concentrations.

Renal dysfunction prolongs the elimination half-life of OR-1896, but it has little effect on the plasma concentration of levosimendan. On the other hand, liver cirrhosis does prolong the elimination half-life of levosimendan, although its effects on production or metabolism of OR-1896 are unknown (Kivikko et al., 2002a,b). Finally, no tolerance to the effects of levosimendan has been observed, even after infusions lasting for as long as 1 week.
as 7 days (Kivikko et al., 2002a,b). Furthermore, no rebound decline in haemodynamic variables has been observed after withdrawal of levosimendan.

3. Levosimendan: molecular mechanisms of action

3.1. Levosimendan as an inotropic agent

Levosimendan is a “Ca\(^{2+}\)” sensitizer with multiple mechanisms of action. It exerts its inotropic effect by increasing the affinity of troponin-C for Ca\(^{2+}\), directly stabilising the Ca\(^{2+}\)-induced conformation of troponin-C, or acting distal to the troponin-C molecule (Fig. 1) (Haikala & Pollesello, 2000). It binds in a Ca\(^{2+}\)-dependent manner to the N-terminal domain of troponin-C, thus magnifying the extent of the contraction produced by troponin-C when it is Ca\(^{2+}\)-activated (Haikala & Linden, 1995). This leads to a positive inotropic effect without impairing diastolic relaxation (Pagel et al., 1994; Haikala et al., 1995; Hasenfuss et al., 1998) or causing cytosolic Ca\(^{2+}\) ion overload, which might provoke cardiac myocyte dysfunction, arrhythmogenesis, and cell death. Indeed, in contrast to other myofilament Ca\(^{2+}\) sensitizers which are bound to the troponin C-Ca\(^{2+}\) complex during both systole and diastole, impairing diastolic function (Hajjar et al., 1997), levosimendan’s binding to troponin C is dependent on cytosolic Ca\(^{2+}\), and it is significantly weaker (causing a minimum Ca\(^{2+}\) sensitization) during diastole, when intracellular Ca\(^{2+}\) levels are low (Haikala et al., 1995). This is the reason why levosimendan enhances myocardial contractility and improves LV diastolic function with relatively low arrhythmogenesis or alteration of myocardial oxygen demands in human myocardium (Lilleberg et al., 1998).

Similar effect on Ca\(^{2+}\) sensitization has also been demonstrated with levosimendan’s active metabolite OR-1896 (Szilagyi et al., 2004). In guinea pig permeabilized myocyte-sized preparations (Szilagyi et al., 2004), the Ca\(^{2+}\)-sensitizing potential of levosimendan was illustrated by an EC\(_{50}\) \approx 8 nM and by a maximal increase in isometric force production (\(E_{\text{max}}\)) \approx 51% (for pCa\(^{2+}\) 6.2). On the other hand, the EC\(_{50}\) for OR-1896 was \approx 36 nM, for an \(E_{\text{max}}\) of \approx 52%. Furthermore, it was demonstrated that levosimendan has an EC\(_{50}\) of \approx 15 nM for the increase of left ventricular pressure signal in guinea pig Langendorff-perfused hearts (\(E_{\text{max}}\), \approx 26%), while the EC\(_{50}\) for OR-1896 in the same model is \approx 25 nM (\(E_{\text{max}}\), \approx 25%).

Despite the strong preclinical evidence that OR-1896 has a similar pharmacodynamic effect as levosimendan (although at relatively high concentrations), it is still unclear whether this is also valid in humans. The long-lasting positive inotropic effect of levosimendan (lasting for several days after a 24-h infusion; Lilleberg et al., 2006) has been explained by the longer semi-life of OR-1896, but there has been no clinical study examining the effect of OR-1896 infusion on myocardial function in humans.

In conclusion, levosimendan exerts its inotropic action mainly by increasing the sensitization of contractile system to Ca\(^{2+}\), although a possible effect on PDE activity and intracellular Ca\(^{2+}\) levels can not be excluded (see next paragraph).

Fig. 1. (A) Levosimendan as an inotropic agent. Levosimendan binds to troponin C during systole, increasing the sensitivity of myofilaments to Ca\(^{2+}\) levels. This phenomenon increases the contractility of myocardium during systole, but it does not affect diastolic function. (B) In more details, levosimendan leads to an opening of the active sites of troponin C, increasing in this way its sensitivity to Ca\(^{2+}\) (Pollesello et al., 1994).
3.2. Levosimendan and phosphodiesterase inhibition

Both levosimendan and its active metabolite OR-1896 appear to have structural similarities with a family of PDE inhibitors. Therefore, it has been hypothesized that levosimendan and OR-1896 may exert part of their action via inhibition of PDE. Indeed, in preliminary ex-vivo experiments conducted 25 years ago (Raasmaja et al., 1991), it was shown that levosimendan inhibits PDE activity selectively and even more potently than milrinone. It was also shown that levosimendan increases cAMP levels in isolated guinea pig intact-hearts and enhances heart rate and the amplitude of the L-type Ca\(^{2+}\)-current (Raasmaja et al., 1991; Edes et al., 1995; Boknik et al., 1997). On the other hand, it has also been suggested that levosimendan had no effect on the intracellular Ca\(^{2+}\) transient, similarly to the effects of β-adrenoreceptor agonists (Hasenfuss et al., 1994). However, a clear dose–effect relation between levosimendan-induced positive inotropy and the intracellular Cа\(^{2+}\) elevation could not be established (Edes et al., 1995; Boknik et al., 1997).

Moreover, several studies have demonstrated that levosimendan either did not increase the intracellular Ca\(^{2+}\) concentration at all (Lancaster & Cook, 1997; Hasenfuss et al., 1998; Brixius et al., 2002) or not to levels high enough to explain its positive inotropic effect (Hasenfuss et al., 1998; Sato et al., 1998; Chen et al., 2003). It is more likely that levosimendan is associated with a moderate elevation of intracellular Ca\(^{2+}\) which may partly contribute to its overall positive inotropic effect in combination with its ability to improve the responsiveness of the contractile system to Ca\(^{2+}\). The extent to which this elevation of intracellular Ca\(^{2+}\) could have any significant side effects (e.g., by inducing arrhythmias) is still unclear.

This controversy about the inhibitory effect of levosimendan and OR-1896 on PDE inhibition was partly addressed by recent reports, suggesting that they are both selective inhibitors of PDE type III (Szilagyi et al., 2004). The half-maximal inhibition of PDE III is achieved at a concentration (IC\(_{50}\)) of 2.5 nM for levosimendan and 94 nM for OR1896 (Szilagyi et al., 2004). On the other hand, half-maximal inhibition of PDE IV is achieved at much higher concentrations of levosimendan (24 μM) or OR-1896 (286 μM) (Szilagyi et al., 2004), which are not achieved in vivo.

Evidence suggests that a marked increase in the IC\(_{Ca,L}\) (and positive inotropism through cAMP signaling) is observed if multiple PDE subtypes are inhibited at the same time, while when only 1 PDE isoenzyme is selectively inhibited, cAMP may presumably be metabolized by other PDE isoenzymes, thereby minimizing a large increase in cAMP at intracellular level (Shahid & Nicholson, 1990; Verde et al., 1999). Although PDE III is the most abundant PDE in the human heart, recent evidence suggest that even a modest hyperactivity of PDE IV may result in an appreciable blunting of the cAMP response to catecholamines, whereas a reduced activity of PDE IV may lead to exaggerated responses in terms of amplitude and duration (Zaccolo, 2006). Therefore, since the inhibition of PDE IV requires significantly higher concentrations of levosimendan or OR-1896 than their maximal free (nonprotein bound) plasma concentration achieved after 24 hr levosimendan infusion (0.2 μg/kg/min), which are 6 nM for levosimendan and 12 nM for OR-1896, it can be hypothesized that in a clinical setting, the selective PDE III inhibition may lead to moderate but not critical elevation of intracellular cAMP (Kivikko et al., 2002a,b). This hypothesis along with the finding that OR-1896 requires concentrations higher (~94 nM) than those observed in clinical practice (~12 nM) to effectively inhibit PDE III (Szilagyi et al., 2004), partly explain previous observations, suggesting that at normal dosage, levosimendan does not induce serious arrhythmias (Lilleberg et al., 2004) and does not have a negative effect on clinical outcome, as other inotropic agents do (Moiseyev et al., 2002).

3.3. Levosimendan and cardiac arrhythmias

It is well known that the use of PDE inhibitors or dobutamine is limited by their arrhythmogenic effect (Packer et al., 1991; Nony et al., 1994). In particular, PDE inhibition induces nonsustained ventricular tachycardias (VT), and increases overall mortality (Nony et al., 1994). In preliminary reports from pigs, levosimendan increased the number of VT and ventricular fibrillation during regional ischemia (du Toit et al., 2001). However, in those studies the elevation of intracellular cAMP in ventricular myocardium was not higher in levosimendan treated animals, compared with controls. Furthermore, in other experimental models of ischemia, levosimendan had no effect on the incidence of ischemia-induced ventricular arrhythmias (Du Toit et al., 1999; Nijhawan et al., 1999). In recent animal studies of ischemia, levosimendan was proved to be clearly superior than the PDE inhibitor milrinone, since it was associated with fewer ventricular premature beats and less incidence of tachycardia or ventricular fibrillation (Papp et al., 2006).

In patients, it seems that levosimendan does not induce significant ventricular arrhythmias (Lilleberg et al., 2004; Mebazaa, 2005), despite the existing evidence that it selectively inhibits PDE III at clinically relevant concentrations (Szilagyi et al., 2004). Indeed, clinical evidence suggests that standard infusion of levosimendan (at a dose 12 μg/kg for 10 min, followed by steady infusion 0.05–0.2 μg/kg/min for 24 h) did not increase the occurrence of nonsustained VT or the frequency of its episodes in patients with heart failure. Furthermore, in the same study it was demonstrated that levosimendan did not increase the QT interval, although the QT interval corrected using Bazett’s formula was slightly prolonged (Toivonen et al., 2000). Levosimendan increased ventricular monophasic action potential duration by 9–17 ms at 50% and by 5–15 ms at 90% levels of repolarization on average. Furthermore, levosimendan was found to increase heart rate by 9 beats/min on average and...
to shorten the sinus node recovery time. Although the underlying mechanisms by which levosimendan affects heart rate are still obscure, it is likely that the activation of baroreceptor reflexes induced by vasodilation could also lead to tachycardia (Harkin et al., 1995).

Furthermore, levosimendan seems to shorten the effective refractory periods in the atrioventricular node by 40–63 ms, in the atrium by 22–33 ms, and in the ventricle by 5–9 ms on average (Toivonen et al., 2000). These observations indicate that levosimendan in short-term administration induces impulse formation and conduction in cardiac nodal tissue, enhances recovery of excitability in the myocardium, and may delay ventricular repolarization.

It is now believed that the effects of levosimendan on the ventricle are not substantial, and the likelihood of provoking serious cardiac arrhythmias is not high (Singh et al., 1999; Toivonen et al., 2000; Lilleberg et al., 2004; Mebazaa, 2005). However, the interpretation of all these clinical trials is particularly difficult, since in most of these studies, patients with documented sustained ventricular arrhythmias were excluded. It is therefore likely that a selection bias was introduced in all these studies. Indeed, a recently presented clinical trial (randomized multicenter evaluation of intravenous levosimendan efficacy versus placebo in the short-term treatment of decompensated heart failure, REVIVE-II) observed a slightly higher incidence of VT in patients treated with levosimendan compared with placebo (25% vs. 17%; Packer, 2005), although this incidence was the same as with dobutamine (survival of patients with acute heart failure in need of intravenous inotropic support [SURVIVE]-W study) (Mebazaa, 2005). Finally, in both SURVIVE and REVIVE-II studies, levosimendan infusion was associated with an increased risk for atrial fibrillation (Mebazaa, 2005; Packer, 2005; Cleland et al., 2006); and this finding requires further evaluation in the future. We should therefore wait for the results of further large randomized clinical trials to conclude whether levosimendan induces dangerous arrhythmias in heart failure patients compared with conventional inotropic agents.

3.4. Levosimendan as a vasodilator

Levosimendan not only increases cardiac performance but has also been shown to induce arteriolar and venous dilatation because of its ability to open ATP-sensitive potassium channels in vascular smooth muscle cells (SMC; Bowman et al., 1999; Pataricza et al., 2000; Kaheinen et al., 2001). In more detail, levosimendan stimulates the ATP-sensitive K⁺ (K_ATP) channel in resistance vessels and the Ca²⁺-activated (K_Ca) and voltage-dependent K⁺ (K_V) channels in large conductance vessels (Pataricza et al., 2003; Yokoshiki & Sperelakis, 2003). Therefore, it leads to the hyperpolarization of the membranes, inhibiting the inward L-type Ca²⁺ (I_Ca,L) current and promoting the forward mode of Na⁺/Ca²⁺ exchanger (Yokoshiki & Sperelakis, 2003; Toller & Stranz, 2006). These mechanisms lead to a decrease of intracellular Ca²⁺-inducing vasorelaxation (Fig. 2).

An additional mechanism by which levosimendan induces vasodilation independently from intracellular Ca²⁺ levels is the reduction of contractile system’s sensitivity to Ca²⁺ in vascular SMC (Bowman et al., 1999; Fig. 2). Finally, levosimendan may also affect vascular tone via its PDE inhibitory effect. At high concentrations (~ 1 mM; Gruhn et al., 1998), levosimendan inhibits PDE, leading to an increase of intracellularcAMP in vascular SMC and vasorelaxation (Haikala & Linden, 1995; Gruhn et al., 1998). Although the inhibitory effect of levosimendan on PDE III is now believed to occur at clinically
relevant concentrations (Szilagyi et al., 2004), the contribution of this mechanism to the overall vasodilatory effect of this drug in humans remains to be defined.

The vasodilatory effect of levosimendan has been demonstrated in several vasculatures including coronaries in animal models (Kaheinen et al., 2001) and humans (Michaels et al., 2005): pulmonary artery (De Witt et al., 2002), systemic arteries and veins (Pagel et al., 1996; Slawsky et al., 2000), saphenous veins (Hohn et al., 2004) and others. Improved contractile performance and vasodilatation leads to a reduction in both preload and after load in the failing heart with reduced myocardial oxygen consumption (Todaka et al., 1996; Michaels et al., 2005). Combined with coronary vasodilatation, this reduction may also have anti-ischemic effects (Lilleberg et al., 1998).

Further to the direct vasodilatory effects of levosimendan itself, very little is known about the effect of its metabolite OR-1896 on vasomotion. In a very recent report (Erdei et al., 2006), it was demonstrated that OR-1896 is a strong vasodilator in both coronary and skeletal muscle arterioles from Wistar rats. In the same study, OR-1896 appeared to be a more potent vasodilator in the coronary than in the gracilis muscle arterioles, an effect not observed with levosimendan itself. It has also been suggested (Erdei et al., 2006) that OR-1896 exerts its vasodilating action again via its interactions with K⁺ channels and especially via interactions with K<sub>ATP</sub> channels in skeletal muscle arterioles and the large conductance K<sub>Ca<sub>2+</sub></sub> channels in the coronaries. It is therefore important to point out that the relative contribution of different K⁺ channels to the OR-1896-induced vasodilation may vary depending on the vessel type and size.

### 3.5. Antiinflammatory and antiapoptotic effects of levosimendan

The failing myocardium is a major source of proinflammatory cytokines (Adamopoulos et al., 2001; Moiseyev et al., 2002) which contribute to the pathophysiology of heart failure (Anker et al., 1997; Adamopoulos et al., 2001; Tentolouris et al., 2004). Cytokines promote the transition from asymptomatic to symptomatic heart failure (Ceconi et al., 1998) since they depress myocardial contractility (Yokoyama et al., 1993), whereas they also promote cardiomyocyte apoptosis and subsequent cardiac remodeling (Krown et al., 1996).

We (Parissis et al., 2004; Trikas et al., 2006) have recently shown that levosimendan administration causes a significant reduction of the circulating proinflammatory cytokine interleukin-6 (lasting for at least 1 month after infusion) and soluble apoptosis mediators, such as the apoptotic marker soluble FAS (sFAS) and Fas ligand in patients with decompensated heart failure. The improved haemodynamics may partly explain the decreased expression of cytokines from the failing myocardium, whereas levosimendan also seems to inhibit the stimuli for myocardial cytokine production and spillover into circulation (Hasenfuss et al., 1995, 1998). Additionally, levosimendan improves systolic function and induces peripheral vasorelaxation, which attenuate peripheral tissue hypoperfusion, leading to down-regulation of cytokine extracardiac production by transcriptional factors, such as nuclear factor kappa B (NF-κB) (Yokoshiki et al., 1997a,b; Adamopoulos et al., 2001). These immunomodulatory effects may lead to improvement of symptoms and echocardiographic markers of cardiac contractile performance (Paraskevaidis et al., 2005; Parissis et al., 2005, 2006).

### 3.6. Levosimendan and ischemic heart disease: cardioprotective effect on ischaemic myocardium

There is evidence that levosimendan may have beneficial effects on ischaemic myocardium since the activation of K<sub>ATP</sub> channels may occur in ischaemic myocardial regions where the intracellular ADP is increased and the ATP is decreased (Kopustinskiene et al., 2004; De Luca et al., 2006a,b). It has been reported that levosimendan opens the K<sub>ATP</sub> channels in both liver (Kopustinskiene et al., 2001) and cardiac (Kopustinskiene et al., 2004) mitochondria, which has been suggested as a cardioprotective mechanism (Oldenburg et al., 2002) linked to the preconditioning in response to oxidative stress (Yokoshiki et al., 1997a,b; De Luca et al., 2006a,b). Indeed, the proposed underlying mechanisms of this effect include the prevention of mitochondrial Ca<sup>2+</sup> overload, the preservation of high energy phosphates, the restoration and stabilization of mitochondrial membrane potential and the regulation of mitochondrial matrix volume (Peart & Gross, 2002; Gross & Peart, 2003). It is therefore possible that the activation of these channels partly explains the cardioprotective effect of levosimendan on ischaemic myocardium (Rump et al., 1994; Du Toit et al., 1999). On the other hand, the very existence of mitochondrial K<sub>ATP</sub> channels has recently been questioned (Hanley & Daut, 2005). Although there is strong evidence for the existence of K⁺ channels in the mitochondrial inner membrane and there is growing consensus that ion channels are involved in the regulation of matrix volume, matrix Ca<sup>2+</sup> and respiratory rate, the properties ascribed to mitochondrial K<sub>ATP</sub> channels on the basis of pharmacological experiments should not be considered as established facts. It is not yet clear whether the mitochondrial inner membrane is endowed with channels that bear any resemblance to surface K<sub>ATP</sub> channels, and alternative hypotheses for the cellular defense mechanisms against ischemic damage are now being considered (Hanley & Daut, 2005).

Further to its possible effect on mitochondrial K<sub>ATP</sub> channels, levosimendan may also activate sarcolemmal K<sub>ATP</sub> channels, which have been associated with both a cardioprotective (Gross & Fryer, 1999) and a possible proarrhythmic effect (Fischbach et al., 2004). Theoretically, this effect of levosimendan on the sarcolemmal K<sub>ATP</sub> channels could lead to arrhythmias as a result of the increased outward repolarizing K⁺ current. This may lead to hyperpolarization of resting membrane potential and shortening of action potential duration, which finally could decrease the effective refractory period (Wilde & Janse, 1994) of myocardial cells promoting arrhythmogenesis. However, despite the observed membrane hyperpolarization (Yokoshiki et al., 1997a,b) and the shortening of action potential duration in isolated cardiomyocytes (Yokoshiki et al., 1997a,b), levosimendan seems to have a rather neutral proarrhythmic effect, although the findings from clinical trials are rather conflicting (see Section 3.3).
3.6.1. Levosimendan and stunned myocardium

Levosimendan may also have beneficial effects on myocardium in patients with myocardial stunning. Myocardial stunning is probably the result of decreased sensitivity of the myofibrils to Ca$^{2+}$ caused by either the generation of oxygen-derived free radicals (radical hypotheses) or by a transient calcium overload on reperfusion (calcium hypotheses; Bolli & Marban, 1999). In these patients systolic dysfunction is usually combined with marked diastolic dysfunction. Calcium sensitization by levosimendan may therefore directly improve the function of stunned myocardium (Soei et al., 1994; Sonntag et al., 2004) especially if we consider that levosimendan improves systolic function without affecting diastolic function (Haikala & Linden, 1995). Furthermore, levosimendan has been shown to improve local coronary blood supply to ischemic myocardial areas (Kersten et al., 2000), increase the coronary flow (Kaheinen et al., 2001) and diminish infarct size (Rump et al., 1994; Kersten et al., 2000), whereas other studies have showed an oxygen-sparing effect of this drug (Kaheinen et al., 2004) and a neutral effect on the energy balance after ischemia/reperfusion (Eriksson et al., 2004).

These antiischemic properties of levosimendan may have an impact on the drug-induced arrhythmogenesis as it has been suggested recently (Papp et al., 2006). This may explain the observation that arrhythmias were not increased when levosimendan was compared with placebo in patients with acute myocardial infarction (Moiseyev et al., 2002) or when administered perioperatively in patients having coronary artery bypass grafting (Nijhawan et al., 1999). However, increased frequency of ventricular arrhythmias was observed when high-dose levosimendan was used in patients with stable ischemic cardiomyopathy (Niemenen et al., 2000), suggesting that attention must be paid when the drug is being used at high doses in patients who have ongoing myocardial ischemia.

4. Haemodynamic effects

It is now believed that levosimendan increases cardiac output by several mechanisms, involving its effects on heart rate, improvement of cardiac performance and vasodilation (Lillegard et al., 1995; Niemenen et al., 2000; Slawsky et al., 2000; Follath et al., 2002; Kivikko et al., 2002a, 2002b). Cardiac output is increased by 0.4–0.8 L/min (by increasing both stroke volume and heart rate), pulmonary capillary wedge pressure (PCWP) is reduced by 4–6 mm Hg and systemic vascular resistance is reduced while transpulmonary gradient remains unchanged (Table 1). In addition, improved cardiac performance has also been suggested by the decrease of circulating levels of amino terminal pro-B-type natriuretic peptide after 24-h infusion of levosimendan (0.1 μg/kg/min) in patients with decompensated congestive heart failure (CHF) and a mean left ventricle ejection fraction at ~25% (Kyrzopoulou et al., 2005; Parissis et al., 2006).

Theoretically, levosimendan could increase cardiac output partly by increasing heart rate (Todaka et al., 1996), an effect observed in patients with ischemic heart failure with New York Heart Association (NYHA) functional class II–IV (Niemenen et al., 2000). Although the exact mechanism of the effect of levosimendan on heart rate is unknown, it seems to be partly mediated by compensatory vasodilation-induced activation of baroreceptor reflexes (Harkin et al., 1995). However, the effect of levosimendan on heart rate is a function of dosage, intravascular volume status and the degree of preexisting impairment of myocardial contractility (Pagel et al., 1997). At a clinical level, 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 (Toller & Stranz, 2006).

4.1. Results from clinical trials

In the levosimendan infusion versus dobutamine in severe low output heart failure (LIDO) study Follath et al., 2002), a randomized double-blinded clinical trial, levosimendan increased cardiac output and reduced PCWP to a greater extent than dobutamine. Levosimendan also reduced systolic blood pressure more and tended to cause more vasodilatation. The haemodynamic effects of levosimendan, unlike those of dobutamine, were not attenuated by the concomitant use of β-blockers. This finding is important, in view of the increasing evidence for the usefulness of β-blockers in the management of severe heart failure.

The dose-ranging study (Niemenen et al., 2000) has demonstrated that all the used dosages of levosimendan caused a greater reduction in PCWP than placebo or dobutamine, while high doses of levosimendan had stronger effect on heart rate and cardiac output. A fall in mean systemic arterial pressure of 5–10 mm Hg was noted with higher doses of levosimendan, while the effects on pulmonary haemodynamics were also reported (Table 1).

Respective improvements of haemodynamics after levosimendan infusion were also observed in the dose escalation study (Slawsky et al., 2000), the 7-day study (Kivikko et al., 2002a, 2002b, 2003), and the bolus study (Lillegard et al., 1995). These haemodynamic effects of levosimendan seem to persist for at least 24 hr after discontinuation of a 24-hr infusion (Kivikko et al., 2002a, 2002b), while there is also evidence that combined infusion of dobutamine and levosimendan may also improve haemodynamics in end-stage heart failure (Nanas et al., 2004).

In conclusion, evidence suggests that levosimendan infusion leads to an improvement of haemodynamics in patients with heart failure, an effect which lasts for several days/weeks after the infusion. However, it is still unclear whether this haemodynamic benefit obtained by levosimendan can be translated into better short- and long-term outcome of these patients.

5. Effects of levosimendan on heart failure symptoms

The effects of levosimendan on heart failure symptoms have been assessed in several studies such as the randomized study on safety and effectiveness of levosimendan in patients with left ventricular failure after an acute myocardial infarct (RUSSLAN) study (Moiseyev et al., 2002), the LIDO study...
Table 1
Levosimendan: clinical trials

<table>
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<tr>
<th>Study</th>
<th>Study protocol</th>
<th>Conclusions</th>
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<tr>
<td><strong>In ischemic heart disease</strong></td>
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<tr>
<td>Moiseyev et al., 2002 (RUSSLAN trial)</td>
<td>Population: 504 patients with left ventricle failure complicating acute myocardial infarction Design: double-blind placebo-controlled trial examining the effect of levosimendan infusion 0.1–0.4 μg/kg/min on composite clinical end points</td>
<td>The mortality was lower in patients treated with levosimendan at 14 and 180 days, although the incidence of ischemia and/or hypotension was similar in all treatment groups</td>
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<tr>
<td>De Luca, 2005</td>
<td>Population: 26 patients with acute myocardial infarction Design: double-blind placebo-controlled trial examining the effect of bolus infusion of levosimendan 12 μg/kg, on haemodynamics and coronary flow velocities after primary angioplasty</td>
<td>Levosimendan induced an improvement of coronary flow reserve and haemodynamics</td>
</tr>
<tr>
<td>Sonntag et al., 2004</td>
<td>Population: 24 patients with acute coronary syndrome Design: double-blind placebo-controlled trial examining the effect of 24 μg/kg levosimendan on left ventricle function after coronary angioplasty</td>
<td>Levosimendan improved the function of stunned myocardium</td>
</tr>
<tr>
<td>De Luca et al., 2006a,b</td>
<td>Population: 52 patients with anterior acute myocardial infarction undergoing primary angioplasty Design: double-blind placebo-controlled trial, evaluating the effects of levosimendan on left ventricular diastolic function</td>
<td>Levosimendan improved the Doppler echocardiographic parameters of left ventricular diastolic function, after primary angioplasty in patients with anterior acute myocardial infarction</td>
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<td><strong>In heart failure patients</strong></td>
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<td>Follath et al., 2002 (LIDO study)</td>
<td>Population: 203 patients with severe chronic heart failure Design: infusion of levosimendan or dobutamine over a period of 24 hr; measurements after 30 hr</td>
<td>Levosimendan reduced systolic blood pressure more and tended to cause more vasodilatation than dobutamine. It increased cardiac output and reduced PCWP to a greater extent than dobutamine; 6 hr after discontinuing infusion, the effects of dobutamine had disappeared, but those of levosimendan persisted</td>
</tr>
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<td>Nieminen et al., 2000 (Dose-ranging study)</td>
<td>Population: 151 patients with NYHA class II to IV heart failure Design: compared 5 different doses of levosimendan with a placebo and with dobutamine when infused over a period of 24 hr</td>
<td>Although both drugs exerted similar effects on stroke volume, all doses of levosimendan exerted a greater reduction in PCWP than placebo or dobutamine; systemic vascular resistance was decreased equally with levosimendan and dobutamine, but further vasodilatation occurred with higher doses of levosimendan; pulmonary vascular resistance declined with higher doses of levosimendan, while the transpulmonary gradient remained unchanged</td>
</tr>
<tr>
<td>Slawsky et al., 2000 (Dose escalation study)</td>
<td>Population: 146 patients with NYHA class III to IV heart failure Design: infusion of levosimendan followed by hourly increments up to a maximum of 0.4 μg/kg/min; patients randomized to levosimendan then received open-label drug for the remainder of the 24 hr; subsequently, patients were randomized to continue levosimendan for 24 hr or to have it withdrawn; further haemodynamic measurements were made at 48 hr</td>
<td>Levosimendan increased stroke volume and cardiac index with significant effects even at the lowest dose; it also increased heart rate by an average of 6 bpm at higher doses, while systemic and pulmonary vascular resistance were declined and mean systemic arterial pressure was dropped by 4 mm Hg; haemodynamic effects persisted or increased over the subsequent 48 hr for those who remained on the infusion, but transpulmonary gradient was not affected; only 70% of patients were titrated to the maximum dose of levosimendan</td>
</tr>
<tr>
<td>Kivikko et al., 2002a,b (7-day study)</td>
<td>Population: 24 patients with NYHA class III to IV heart failure Design: randomized to an infusion of 0.05 or 0.1 μg/kg/min for 7 days during which time, heart rate, blood pressure and ECGi were monitored</td>
<td>Metabolite concentrations reached their peak about 24 hr after cessation of therapy and were still detectable at therapeutic levels 2 weeks later; heart rate was increased by up to 18 bpm and 26 bpm, respectively, while blood pressure dropped by 6 mm Hg and 11 mm Hg, and returned to baseline within 3 days of cessation of therapy in contrast to the heart rate, which remained increased even 14 days after cessation of infusion</td>
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<tr>
<td>Lilleberg et al., 1995 (Bolus study)</td>
<td>Population: 24 patients with severe chronic heart failure Design: 5-min bolus infusions of levosimendan ranging from 0.25 to 4 mg</td>
<td>Heart rate and cardiac output were increased while the filling pressures were reduced; the peak was reached after 10 min and the results were dose related</td>
</tr>
<tr>
<td>Kivikko et al., 2003</td>
<td>Population: 146 patients with decompensated heart failure Design: randomized placebo controlled trial, using levosimendan infusion 6 μg/kg bolus, followed by 0.1–0.4 μg/kg/min continuous infusion for 24/48 hr</td>
<td>The haemodynamic effects of levosimendan maintained during 48-hr continuous infusion and for at least 24 hr after discontinuation of a 24-hr infusion</td>
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Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study protocol</th>
<th>Conclusions</th>
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</table>
| Nanas et al., 2004           | Population: 18 patients with end-stage heart failure, refractory to dobutamine and furosemide  
Design: compared the infusion of dobutamine (10 μg/kg/min) with bolus infusion of levosimendan  
6 μg/kg followed by 0.2 μg/kg/min infusion as adjunctive therapy  
| This study evaluated the magnitude and duration of haemodynamic effects of combined infusion of  
dobutamine and levosimendan in end-stage heart failure, and demonstrated that the combined treatment  
improves haemodynamics and symptoms for 24 hr |

| Mebazaa, 2005;  
Cleland et al., 2006 (SURVIVE-W study) | Population: 1327 patients with severe heart failure  
(ejection fraction < 30%)  
Design: randomized controlled trial, comparing the effect of levosimendan (n = 664, with bolus 12 μg/kg followed  
by stepped dose regimen of 0.1–0.2 μg/kg/min for 24 hr) and dobutamine (n = 663, 5 μg/kg/min for 24 hr or more)  
on clinical end points  
| Although there was a trend for an improved short-term survival after levosimendan infusion, this was only from  
the period of haemodynamic efficacy of the drug, and it was not significantly better than dobutamine; patients  
who received levosimendan were more likely to experience atrial fibrillation (9.1% vs. 6.1%) and less likely to  
show worsening of heart failure (12.3% vs. 17%) compared with dobutamine |

| Packer, 2005;  
Cleland et al., 2006 (REVIVE-II study) | Population: 600 patients with acute decompensated heart failure and ejection fraction < 30%, unresponsive to diuretics and vasodilators  
Design: multicenter, randomized placebo controlled trial, examining the effect of levosimendan (initial bolus, 12 μg/kg followed  
by a stepped dose regimen of levosimendan, 0.1–0.2 μg/kg/min for 24 hr) on a complex clinical end point;  
the treatment was on top of standard therapy; patients followed-up for 4 days after the end of infusion  
| The primary complex end-point was achieved  
(19.4% experienced improvement with levosimendan vs. 14.6% in placebo, p = 0.015); although plasma BNP  
was decreased and the duration of hospitalization was shortened by ~2 days (7.9 vs. 8.9 days in  
placebo, p = 0.001), this was not accompanied by a reduction of mortality; furthermore, there were more  
reports of hypotension (50% vs. 36%), VT (25% vs. 17%) and atrial fibrillation (8% vs. 2%) in  
levosimendan-treated patients compared with placebo |

| Cleland et al., 2004;  
Zairis et al., 2004 (CASINO study) | Population: 299 patients with decompensated low-output heart failure (ejection fraction < 35%)  
Design: patients randomized to receive 24 hr infusion  
with levosimendan or placebo or dobutamine; the primary end-point was the composite of or rehospitalization because  
of heart failure deterioration death  
| The study was designed to recruit 600 patients, but it  
was stopped after 299 patients had been recruited, as  
a result of the clear superiority of levosimendan versus  
the other treatments (6 months mortality was 18% for  
levosimendan, 42% with dobutamine and 28.3% for placebo) |

PCWP: pulmonary capillary wedge pressure; BNP: NT-pro-Brain Natriuretic Peptide.

According to (Follath et al., 2002), the dose escalation study (Slawsky et al., 2000) and others.

5.1. Results from clinical trials

The RUSSLAN study (Moiseyev et al., 2002) randomized 504 patients with acute pulmonary edema after myocardial infarction to 4 different 6-hr dosing regimens of levosimendan or placebo in addition to conventional background therapy with the exception of other intravenous inotropic agents. The objective of the study was to examine the safety of levosimendan in this high-risk population, targeting the risk of ischemia and hypotension. Levosimendan did not exacerbate these problems except at the highest dose. Overall, levosimendan did not affect symptoms. However, worsening heart failure was less likely with levosimendan than with placebo at 6 hr and 24 hr. Also, patients treated with levosimendan experienced less dyspnea and fatigue.

Similarly, in the dose escalation study (Slawsky et al., 2000), the symptoms were more often improved on levosimendan than on placebo at the end of the 6-hr, double-blind phase. Similar trends were observed for fatigue. However, in the LIDO study (Follath et al., 2002), nonsignificant trends towards greater improvement in breathlessness and fatigue were noted among patients receiving levosimendan compared with dobutamine.

The effect of levosimendan on symptomatic relief in heart failure patients was also examined in the recently presented REVIVE-II trial (Packer, 2005), which was actually the first large, prospective, randomized, double-blind, controlled trial comparing the effects of levosimendan plus standard therapy to the effects of standard therapy alone over the clinical course of patients with acute decompensated heart failure. Importantly, the REVIVE-II showed an improvement of the composite end-point (Table 1) compared with placebo. The 3-stage “composite end-point” of this study consisted of 3 ranking clinical features: “improved” (defined as moderately or markedly improved patient global assessment at 6 hr, 24 hr, 5 days and no worsening), “unchanged” (defined as neither improved nor worse) or “worse” (defined as death from any cause, persistent or worsening heart failure requiring intravenous medications such as diuretics, vasodilators or inotropes at any time or moderately/markedly worse patient global assessment at 6 hr, 24 hr and 5 days). In the REVIVE II it was demonstrated that levosimendan improves symptoms, decreases the duration of hospitalization and decreases NT-pro-brain natriuretic peptide (BNP) levels (Table 1).

Although the outcome of clinical trials regarding the effect of levosimendan on heart failure symptoms is still controversial, it seems that levosimendan is indeed a therapeutic option to relief symptoms of heart failure, improving in this way the quality of life in these patients.
6. Effects of levosimendan on morbidity and mortality

The initial evidence suggested that levosimendan is superior to any other inotropic agent currently used in clinical practice, regarding its effects on morbidity and mortality (De Luca et al., 2006a,b). Indeed, in the RUSSLAN study (Moiseyev et al., 2002), the composite outcome of death or worsening heart failure at 24 hr was significantly reduced from 8.8% to 4.0%. All-cause mortality at 14 days was again significantly reduced from 19.6% to 11.7%, whereas at 180 days, mortality on levosimendan was 22.6% compared with 31.4% on placebo. The reduction in mortality was similarly independent of the dose of levosimendan used in the study. Similar effects were also observed in the LIDO study (Follath et al., 2002), since 1 month after levosimendan infusion, there was a significantly lower mortality with levosimendan than with dobutamine and a reduction in the composite endpoint of death or worsening heart failure. In addition to improving haemodynamic performance, lower mortality was seen in the levosimendan group than in the dobutamine group for up to 180 days (26% vs. 38%, 0.57 [0.34–0.95]; p=0.029). A reduction in the composite outcome (death or hospitalization with heart failure or an increase in days alive and out of hospital) during 6 months of follow-up was also observed. The results of that study have led to much speculation. Dobutamine may have had an adverse effect on survival. Acute exposure to powerful adrenergic stimulants may not only provoke arrhythmias but also accelerate programmed cell death of cardiac myocytes, worsening both short-term and long-term outcome. On the other hand levosimendan might exert a sustained beneficial effect on haemodynamics, with possible secondary neuroendocrine benefits with relatively lower hazards of arrhythmogenesis, cellular Ca2+ overload, and induction of cell death.

6.1. Results from recent and ongoing clinical trials

The SURVIVE study (Mebazaa, 2005) is actually the first clinical trial examining the short- and long-term survival after levosimendan infusion in high-risk patients with severe heart failure (ejection fraction <30%), compared with dobutamine (Table 1). The major end point was 180-day all-cause mortality; and despite the trend towards greater improvements with levosimendan early after the end of infusion, this did not reach significance (Table 1). Although the full details of the study have not been published yet, it seems that levosimendan also reduced BNP to a greater extent than dobutamine during the first week after infusion. Furthermore, it was associated with lower risk of heart failure worsening but higher risk for atrial fibrillation compared with dobutamine. Interestingly, the proportion of other side effects, such as hypotension and VT, was similar in both study groups (Mebazaa, 2005).

On the other hand, in the REVIVE-II study (Packer, 2005), levosimendan had no effect on 90-day mortality, although it seems that it induced some side effects, such as hypotension and arrhythmias (Table 1). However, it is important to point out that the REVIVE-II was not designed to examine the effect of levosimendan on mortality, whereas the study population consisted of relatively young (mean age, 63 years) patients, mainly males (73%). Therefore, we should wait for publication of these results before any definite conclusion is made.

In a third clinical trial, the calcium sensitizer or inotrope with none in low-output heart failure (CASINO) study (Zairis et al., 2004), a clear benefit of levosimendan on 6 months of survival was demonstrated in patients who received levosimendan compared with placebo (Table 1) (Cleland et al., 2004). The superiority of levosimendan in the CASINO study was so clear that the study was stopped early after recruitment of 299 patients (out of 600 patients scheduled to be recruited in the initial study design; Cleland et al., 2004).

A more critical view of the existing data regarding the impact of levosimendan on mortality in heart failure leads to the conclusion that the high heterogeneity of the few published studies does not allow any safe conclusions for the moment. Previous studies comparing the effects of levosimendan versus dobutamine were referred mainly to patients with severe chronic heart failure, who were more likely to be under treatment with beta-blockers, which seems to interact favorably with levosimendan compared with dobutamine (Follath et al., 2002). The rather conflicting results of the recently published clinical trials are reflected in a recent meta-analysis (Cleland et al., 2006) which indicated a nonsignificant trend towards better short-term survival with levosimendan compared with placebo (OR [95% CI]: 0.79 [0.58–1.08]) and a borderline significant difference compared with dobutamine (OR [95% CI]: 0.75 [0.60–0.93]).

In conclusion, the ability of levosimendan to improve short-or even long-term survival in patients with severe heart failure is still a topic of controversy, and further studies are needed to document such an effect.

7. Side effects of levosimendan—interactions with other drugs

Levosimendan is generally well tolerated by patients. However, decrease in vascular resistance, which is induced by the drug, can lead to various haemodynamic effects. Hypotension is probably one of the most common side effect observed after levosimendan administration in the clinical practice (Nieminen et al., 2000; Mebazaa et al., 2005; Packer, 2005). Indeed, REVIVE-II study (Packer, 2005) reported a higher incidence of hypotension in the levosimendan group compared with the placebo group (50% vs. 36%). Consequently hypotension may cause myocardial ischemia, cardiac arrhythmias, and hypoxemia. However, these side effects are not common when the treatment remains within the recommended doses (Nieminen et al., 2000; Moiseyev et al., 2002). The vasodilatatory effects of the drug may be responsible for headache (5% of patients), dizziness (1–10% of patients), and nausea (1–10% of patients) (Slawsky et al., 2000; Sundberg & Lehtonen, 2000; Follath et al., 2002; Moiseyev et al., 2002).

Levosimendan may also affect cardiac rhythm. It may increase sinus rate, shorten sinus node recovery time and decrease atrioventricular nodal conduction interval (see Section 3.3; Toivonen et al., 2000). Levosimendan may prolong the
rate-corrected QT interval, an effect which seems to be dose related (Nieminen et al., 2000) and largely also dependent on the patient’s clinical profile (Lilleberg et al., 1995; Sundberg et al., 1995). Despite this proarrhythmic potential of levosimendan, most of the clinical studies provided no evidence of increased life-threatening ventricular tachyarrhythmias after levosimendan administration in the clinical practice (Lilleberg et al., 2004). However, 2 recent clinical trials, the REVIVE-II and SURVIVE studies, have shown that patients receiving levosimendan were more likely to experience atrial fibrillation compared with placebo and dobutamine (Mebazaa, 2005; Packer, 2005).

Another interesting issue with levosimendan is its interaction with other heart failure drugs. Most patients with heart failure being treated with levosimendan are usually taking other routine heart failure drugs concomitantly such as ACE inhibitors, diuretics, nitrates, beta-blockers and digoxin. In the LIDO study (Follath et al., 2002) 89% of patients receiving levosimendan were using ACE inhibitors, 76% were using digoxin and 95% were using diuretics. However, clinical studies so far have not reported serious interactions when levosimendan was used within the recommended dose range. Similarly, concomitant use of levosimendan and beta-blockers was shown to have beneficial or neutral effects on the inotropic efficacy of the drug (Haikala et al., 1997; Follath et al., 2002; Lehtonen & Sundberg, 2002), while the actions of dobutamine were attenuated (Follath et al., 2002). Furthermore, the combination of levosimendan with angiotensin converting enzyme inhibitors has been associated with only minor decreases in mean arterial blood pressure when levosimendan was used within the recommended dose range (Antila et al., 1996; Nieminen et al., 2000). On the other hand its combination with nitrates increased heart rate by 40 beats/min in healthy subjects during an orthostatic test (Sundberg et al., 1995) but produced only marginal decreases in systolic blood pressure (5 mm Hg) and minor increases in heart rate (4 beats/min) in patients with acute myocardial infarction (Moiseyev et al., 2002). Finally no increase in heart rate and no effect on blood pressure were observed when coadministered with furosemide, amiodarone (Nanas et al., 2004) and calcium antagonists (Poder et al., 2003). Taken together, all these data suggest that levosimendan does not appear to have any serious interactions with the currently used medication in heart failure. And this may provide an important advantage against dobutamine, especially when beta-blockers are co-administered.

8. Conclusions

Levosimendan is a $Ca^{2+}$ sensitizer in myocardium and $K^{+}$/ $K_{Ca^{2+}}$- $K_{ATP}$ channel opener in vascular SMC that has a dual inotropic and vasodilatory effect. It provides both symptomatic and haemodynamic improvement within a few hours of treatment initiation, while these benefits are achieved with a minimal increase of myocardial oxygen requirements and without impairing diastolic relaxation. Furthermore, it seems to have beneficial effects in ischemic heart disease, since further to its effect as a vasodilator, it also seems to have direct cyto-protective effects on ischemic myocardium, while it also has anti-inflammatory and antiapoptotic properties.

Despite the initial reports for a positive effect of levosimendan on short- and long-term survival in patients with severe heart failure, the results of the recently presented large-scale clinical trials provided rather controversial results. Although levosimendan is considered to induce fewer arrhythmias than classic inotropes, recent studies suggested that levosimendan infusion may be associated with higher incidence of atrial fibrillation in patients with heart failure.

In several countries, levosimendan is already routinely used in patients with heart failure requiring inotropic support. If future studies confirm its beneficial effect on mortality, it is likely to become the inotropic agent of first choice in severe heart failure in the near future.

References


II and phase III clinical studies in cardiac failure. *Am J Cardiol* 83(12, Supplement 2), 16.


