Levosimendan

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KEY POINTS

- Traditional inotropes mobilise myocardial calcium, increasing contractility.
- Levosimendan is a novel inotrope that sensitises the myocardium to calcium, increasing contractility without increasing oxygen consumption.
- Levosimendan also exhibits a host of other beneficial effects on the circulatory system, kidneys and liver via K+ and myocardial ATP channel activation.
- There is not enough evidence at present to recommend routine levosimendan use over standard inotrope therapy.
- Levosimendan is a useful inotrope in patients with Takotsubo cardiomyopathy.
- Several other novel inotropes are either in development or are the focus of renewed interest, including the ancient Chinese traditional medicine Shenfu.

INTRODUCTION

Positive inotropes are drugs that enhance myocardial contractility independent of changes in heart rate or loading conditions. Therapeutic inotropic manipulation has a rich history. The ancient Chinese "Shenfu" formula has been used in Chinese traditional medicine for more than 2000 years to manage manifestations of heart failure: strengthening a deficient Yang 阳 (promoting water metabolism) and invigorating a deficient Qi 气 (increasing blood circulation).[1]

In 1775, the physician and botanist William Withering introduced the use of digitalis to treat the symptoms of heart failure,[2] whereas the latter half of the 20th century saw the introduction of the beta-adrenergic agonists, such as dopamine and dobutamine, followed by nonsympathomimetic phosphodiesterase (PDE) inhibitors.[3] Both catecholamines and PDE inhibitors act as myocardial calcium mobilisers and therefore share many of the same side effects.[4] The use of inotropes may be lifesaving in the management of acute cardiogenic shock, but their use has been consistently associated with an increased morbidity and mortality.[2] This has led to the search for alternative inotropic strategies, culminating in the introduction of the myocardial troponin calcium sensitiser, levosimendan, in the 1990s, which is still currently the only agent available in this class.[3]

In this review, we focus on levosimendan and outline the current evidence available regarding its safety and efficacy. We also describe several new experimental positive inotropic agents with novel pharmacodynamic mechanisms that may become available in the coming years. Finally, we outline how the abovementioned Shenfu formula, in modern intravenous form, has appeared recently in Western medical literature for use in septic shock and heart failure.[5]

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LEVOSIMENDAN

Presentation

Levosimendan (Figure 1) is the active R enantiomer of simendan, with dextrosimendan (the S enantiomer) being 47 times less potent.[6] The drug is usually presented in vials containing 2.5 mg/mL of a clear yellow solution. It is minimally water soluble.

Mechanisms of Action

Levosimendan acts primarily by increasing calcium sensitisation in the myocardium, thereby improving both systolic contraction and diastolic relaxation. It also acts on potassium channels in vascular smooth muscle as well as ATP-sensitive potassium channels in the mitochondria (Table 1; Figures 2 and 3).

Pharmacokinetics of Levosimendan

Absorption and Distribution

Levosimendan is normally administered in its intravenous form; however, oral and transdermal preparations also exist. The oral presentation has a bioavailability of 85%. It is 98% protein bound, has a pKa of 6.3 and a volume of distribution of 0.2 L/Kg.

Metabolism and Excretion

Ninety-five percent of levosimendan is conjugated with glutathione to inert cysteine and renally excreted. The residual 5% is metabolised in the intestine to a biologically active metabolite, OR-1855, which is then N-acetylated to OR-1896. Although the elimination half-life of levosimendan is 1 to 1.5 hours, the same property for OR-1896 may exceed 80 hours.

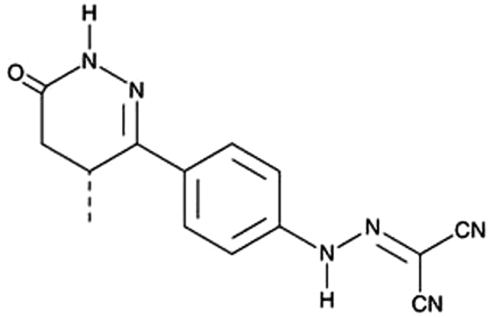

Figure 1. Structure of levosimendan.

Cellular Mechanism of Action	Result
Calcium sensitisation	Improved systolic contraction and diastolic relaxation.[6] In the presence of calcium, levosimendan binds to the N terminal of cardiac troponin C and stabilises calcium-induced conformational change, increasing actin-myosin cross-bridge formation and thus enhancing systolic contraction (Figures 2 and 3). The opposite happens in diastole as a result of reduced calcium concentration, improving relaxation. Calcium sensitisation as opposed to mobilisation increases contractility without increasing myocardial oxygen consumption. There is also some PDE inhibitor action that is thought to contribute to positive inotropy.[7,8]
Potassium channel activation	Levosimendan also binds and opens potassium channels on vascular smooth muscle sarcolemma; potassium influx hyperpolarises the cell and aids vasorelaxation and vasodilation by reducing intracellular calcium.[9]
Mitochondrial ATP-sensitive potassium channel activation	Opening ATP-sensitive potassium channels on mitochondrial membranes. Resultant hyperpolarisation reduces calcium influx and oxidative phosphorylation, reducing metabolism during ischaemia and, in myocardial cells, contributing to ischaemic preconditioning.[10,11]

Table 1. Levosimendan's Mechanisms of Action

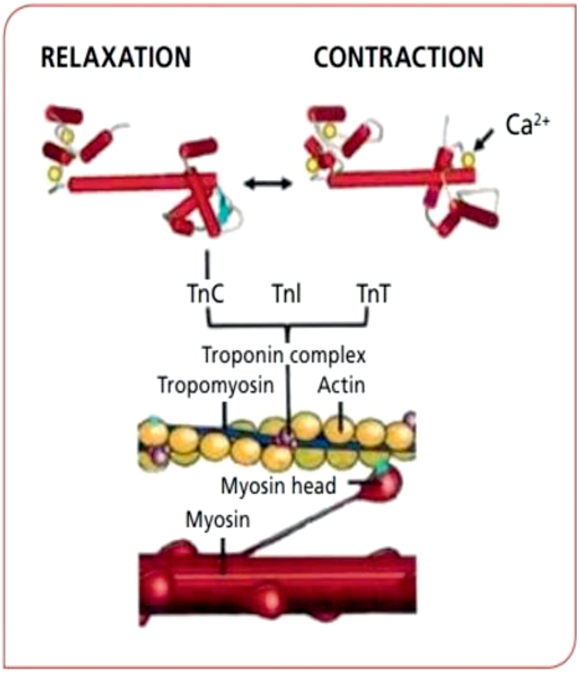

Figure 2. Role of troponin C in the mechanism of myocyte contraction. Image reproduced with permission from Orion Pharma.

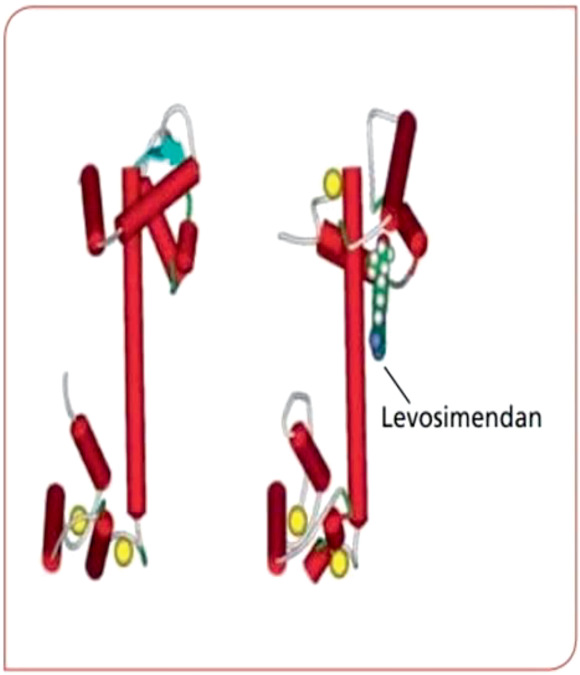

Figure 3. Levosimendan selectively binds to calcium-saturated cardiac troponin C. Image reproduced with permission from Orion Pharma.

The resultant accumulation of OR-1896 is responsible for the sustained effects of the drug after discontinuation of an infusion, often for up to 7 to 9 days. Therefore, the drug is usually administered as a 24-hour infusion.[6]

Pharmacodynamics of Levosimendan

The effect site of most interest for levosimendan is the heart, where it affects inotropy and lusitropy, among others (Table 2). It also exerts positive effects on the kidneys, liver, lungs and diaphragm (Table 3).

Cardiac Effect	Description
Chronotropy	Increased, most pronounced with bolus dosing or higher infusion rates; presumed reflex compensation for vasodilatation[10]
Inotropy	Dose-dependent increase in stroke volume and thus cardiac output without significant increase in oxygen consumption[12,13] This effect not impaired by existing therapy with beta-blockade[14]
Lusitropy	Improves diastolic relaxation in healthy and heart failure animal models Also improves diastolic function after cardiac surgery and after ischaemic myocardial stunning[15]
Vasodilatation	Widespread (systemic, pulmonary, coronary, cerebral and portal) vasodilatation[10] Decreased systemic and pulmonary vascular resistance and mean arterial pressure along with improved cardiac output and better LV and RV arterial coupling[16]
Cardio-protection	Favourable effects on coronary blood flow and afterload (described above) to improve myocardial oxygen supply and demand balance Consensus opinion also suggests short-term cardioprotection via ischaemic preconditioning (reducing ischaemia-reperfusion injury and reducing infarct size, see Table 1) and long-term protection (likely by drug's ability to mitigate myocyte apoptosis and remodelling)[17]

Table 2. Cardiac Pharmacodynamic Effects of Levosimendan

Organ Affected	Description
Renal	Some ischaemia and reperfusion injury protection–like cardiac effect, likely via mitochondrial K+ channel activation Improvement in glomerular filtration rate (GFR) via selective afferent arteriolar vasodilation (contrast with dopamine, which dilates afferent and efferent arterioles, increasing renal blood flow without an increase in GFR)[15]
Liver	Hepatic portal and arterial vasodilatation protect liver from ischaemia Apoptosis reduction also provides some protection from reperfusion injury[15,18]
Lung	As per kidney and liver—evidence of lung protection from ischaemia and reperfusion injury in experimental models of sepsis and myocardial ischaemia implicating antiapoptotic and anti-inflammatory effects
Diaphragm	Levosimendan also shown to improve calcium sensitivity in diaphragmatic muscle and to improve contractile efficiency[15]

Table 3. Noncardiac Pharmacodynamic Effects of Levosimendan

Side Effects of Levosimendan

Levosimendan is usually well tolerated with few side effects, but the associated vasodilatation may cause dizziness and headaches and may precipitate hypotension. It is a positive chronotrope and causes tachycardia, enhances AV nodal conduction and reduces the refractory period. High doses prolong the QT interval. There is conflicting evidence regarding the drug's propensity to cause arrhythmia, specifically atrial fibrillation.[10]

Indications and Evidence

Acute Heart Failure

In the 2016 European Society of Cardiology guidelines,[19] inotropes are recommended in acute heart failure (AHF) for patients with hypotension (systolic blood pressure of <90 mm Hg) and/or signs and symptoms of hypoperfusion. Levosimendan (or a PDE inhibitor) is recommended when beta-blockade is felt to be contributing to that hypoperfusion. The guidelines recommend the addition of a vasopressor in patients with a systolic blood pressure <85 mm Hg to offset the vasodilatory effects.

Two early studies compared levosimendan to dobutamine in AHF: LIDO and SURVIVE.[20] The small LIDO trial demonstrated that levosimendan's mechanism of action is independent of beta-blockade and it signalled a mortality benefit. This was further evaluated in the more comprehensive SURVIVE trial, which showed an early decrease in mortality but no difference in longer term follow-up.

The REVIVE I and II studies evaluated levosimendan's efficacy in treating symptoms of heart failure, showing improved symptoms and shorter hospital stays in patients receiving levosimendan, albeit with a trend to increased arrhythmias (atrial fibrillation and ventricular tachycardia).[20] A recent expert review of the role of levosimendan in AHF complicating acute coronary syndrome asserted that levosimendan offers potential benefits in this setting. However, the only large randomised

controlled trial evaluating levosimendan after myocardial infarction, the RUSSLAN trial, was primarily designed to evaluate safety and not efficacy for this indication.[21]

Other than the trials mentioned above, there is a paucity of evidence regarding the use of levosimendan in cardiogenic shock, despite its theoretically favourable characteristics. In the above expert review, the authors recommend avoiding bolus dosing and administering a 24-hour infusion at 0.05 to 0.1 μg/kg/min with the option of increasing to 0.2 μg/kg/min for 1 hour if a more rapid effect is required. As mentioned earlier, concurrent use of a vasopressor may be required.

Advanced Heart Failure

Levosimendan consistently leads to a rapid and sustained decrease in brain natriuretic peptide (BNP) in clinical trials.[21] Recent randomised, controlled clinical trials have evaluated using levosimendan on a repetitive basis in patients with advanced heart failure (New York Heart Association III or IV symptoms). The LION-Heart, LAICA and Levo-Rep trials evidenced the safety and tolerability of repetitive use levosimendan in the outpatient setting. All 3 trials showed reductions in NT-pro-BNP levels and trends to a reduction in heart failure–related admissions or readmissions as well as mortality.[22]

Takotsubo Cardiomyopathy

Levosimendan's properties would seem to confer unique benefits in the management of cardiogenic shock caused by catecholamine-mediated Takotsubo cardiomyopathy.[3] Two small studies have shown accelerated recovery of ejection fraction and decreased length of hospitalisation, along with feasibility and safety, when levosimendan was administered to these patients, although a mortality benefit was not clear.[23,24]

Renal Perfusion

Evidence is conflicting, but levosimendan appears to have beneficial effects on renal function. These benefits may be mediated mainly through improved cardiac output and decongestion of the venous circulation of the kidney.[22,25]

Pulmonary Hypertension

The pharmacodynamics of levosimendan suggest a benefit in treating pulmonary hypertension and right heart failure, but there is limited evidence to support this.[26] A recent meta-analysis studying the efficacy and safety of levosimendan showed some short-term efficacy in managing RHF of varying aetiology, albeit in small studies.[27]

Septic Cardiomyopathy

Septic shock is often characterised by vasoplegia, but this may be accompanied by septic cardiomyopathy (SCM). SCM is acute cardiac dysfunction, unrelated to ischaemia, in a patient with sepsis. It may complicate up to 60% of cases of septic shock.[28]

The most recent Surviving Sepsis Campaign international guidelines recommend dobutamine as the first-line inotrope in patients with measured or suspected low cardiac output assuming adequate left ventricular filling pressures.[29] This is despite the fact that adrenergic overstimulation of the myocardium contributes to the pathophysiology of SCM and indeed the observation that esmolol, a β1 antagonist, may paradoxically improve outcomes in SCM.[30] Levosimendan would therefore seem to be a promising inotropic drug in the context of SCM, although the evidence is not conclusive. A small study comparing levosimendan to dobutamine in sepsis after 48 hours of conventional therapy showed that levosimendan increased CO and decreased pulmonary congestion as well as increased lactate clearance, mucosal perfusion and renal function without an increase in vasopressor requirements—all factors that remained unaltered by dobutamine.[31]

The recent LeoPARDS trial, on the other hand, examining early administration of levosimendan in septic shock, was not able to show a difference in mortality or organ dysfunction (the primary endpoint) in patients given conventional therapy for septic shock when compared with the control group (conventional therapy plus a placebo infusion). This was accompanied by a higher incidence of supraventricular tachyarrhythmia and a reduced likelihood of successful extubation.[30] The Surviving Sepsis Guidelines therefore question the systematic use of levosimendan and continue to prefer dobutamine.[29]

Cardiac Surgery

Levosimendan's effects make it theoretically useful in the context of cardiac surgery. It has been extensively evaluated perioperatively, with most studies focusing on patients with decreased left ventricular ejection function (LVEF). Multiple small studies have shown levosimendan to be associated with improved haemodynamic parameters, a reduction in low cardiac output states postoperatively, decreased intensive care unit (ICU) lengths of stay and a decreased necessity for additional inotropic agents.

Several meta-analyses have demonstrated significant reductions in mortality and kidney injury in cardiac surgery patients with reduced LVEF.[32] These findings led a panel of European experts to recommend a preoperative infusion of levosimendan in patients with "generally compromised myocardial function, including right ventricular function," beginning 1 day preoperatively and continuing for 24 hours.[33]

The picture, however, has been clouded by the conclusions of 3 subsequent, large, randomised, controlled trials: the LEVO-CTS, CHEETAH and LICORN trials.[32] All 3 compared levosimendan to placebo in cardiac surgery patients with low ejection fraction. None of these trials showed a significant difference in mortality, with the CHEETAH trial being stopped early for futility. LEVO-CTS and LICORN also studied ICU hospital length of stay, the need for renal replacement therapy and mechanical cardiac support. They did not find a significant difference in these outcomes. LICORN also found no significant difference in low cardiac output states or duration of catecholamine use.[34] A more recent meta-analysis, which included these newer trials, concluded that the evidence does not currently support either prophylactic or therapeutic administration of levosimendan in cardiac surgery.[35]

OTHER NOVEL INOTROPIC AGENTS

There are a small number of novel inotropic agents, such as omecamtiv mecarbil and istaroxime, that have been developed recently and are undergoing study.[36-38] Perhaps the most relevant globally might be Shenfu.

Shenfu injection (SFI) has a long history of use in China in the treatment of 厥脱, the Chinese traditional medical manifestation of shock, and as such cannot be considered to be novel. However, SFI has recently begun to appear in Western medical literature.[39]

It is a traditional Chinese medicine composed of extracts of red ginseng roots (*Radix Ginseng rubra*) and aconite roots (*Radix Aconitum Carmichaelii*) (Figure 4). These components yield a preparation with multiple active ingredients.[40,41]

There are positive inotropic effects, including some direct beta- and alpha-agonism, as well as augmented catecholamine release, upregulation of β-adrenoreceptors and anti-inflammatory and antioxidant properties.[42] Agonism of myocardial β-receptors is obviously not a novel inotropic strategy. However, some of the active ingredients in the mixture have also been shown to upregulate the expression of SERCA2a, decreasing myocardial cytosol calcium levels and protecting against myocardial apoptosis by inhibiting myocardial caspases, as well as decreasing plasma levels of tumour necrosis factor–α and other cytokines.[43,44]

Despite an extensive volume of publications involving SFI in Chinese medical literature, it is difficult to draw significant conclusions relevant to Western medicine. This is due to disparate methodologies and interpretations and the way in which Chinese traditional medicine is combined with established Western medical techniques in clinical practice in China. A recent randomised controlled trial studied the use of SFI following the return of spontaneous circulation after in-hospital cardiac arrest and showed a significant improvement in outcomes, including greater rates of survival and favourable neurologic outcomes.[45] A 2021 meta-analysis of SFI in the management of heart failure concluded that it may be clinically effective and safe but advised the need for a more conclusive evidence base.[46]

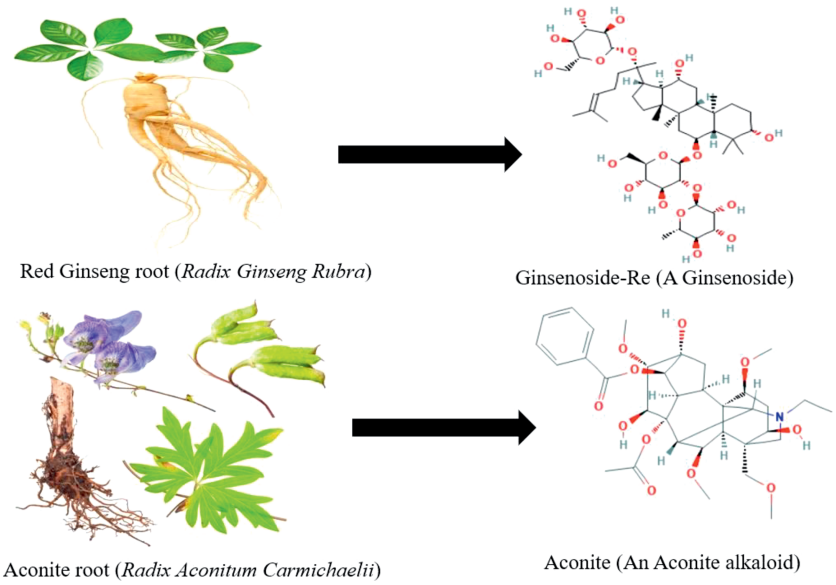

Figure 4. Components of Shenfu. Courtesy of Getty Images.

CONCLUSION

Novel inotropic strategies have been in development in recent years to produce the desired clinical effects of improved left ventricular performance without the associated common adverse effects of traditional inotropic agents. Levosimendan entered clinical practice in 2001 but remains the only new inotropic agent currently available, with no conclusive evidence demonstrating a clear superiority or inferiority over standard inotropic drugs.[47] There is evidence to suggest that standard inotropic drugs can increase mortality, and we have presented cases in which it may be prudent to use levosimendan as a first-line inotrope. The β-blocked patient suffering AHF or early Takotsubo syndrome are cases in point. However, using familiar and more established agents, backed by an evidence base and existing clinical guideline, will be the default option for most situations.

Other new inotropic agents are in development or in early clinical trials but are unlikely to be introduced into clinical practice soon. SFI, a traditional Chinese medicine that has long been used for a variety of cardiovascular indications in China, is now appearing more frequently in international medical literature. Although this ancient formula is not a novel inotrope, it is new to Western medicine, notwithstanding the fact that some of its effects likely derive from β-agonism. The use of Shenfu requires more robust evidence before it can be considered for use in Western medicine.

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