Levosimendan use in several scenarios of Acute Heart Failure

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Abbreviations

AHF – Acute Heart Failure
AMI – Acute Myocardial Infarction
ARDS – Acute Respiratory Distress Syndrome
ATP – Adenosine Triphosphate
cAMP – Cyclic Adenosine Monophosphate
CABG – Coronary Artery Bypass Grafting
CO – Cardiac Output
HF – Heart Failure
LIDO – Levosimendan Infusion versus Dobutamine
PCI – Percutaneous Coronary Intervention
PDE – Phosphodiesterase
PCWP – Pulmonary Capillary Wedge Pressure
REVIVE – Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy
SURVIVE – Survival of Patients with Acute Heart Failure In Need of Intravenous Inotropic Support
TnC – Troponin C
TnI – Troponin I

Summary

In countries where it is available, early levosimendan infusion can be considered for patients who remain symptomatic with dyspnea at rest despite initial therapy, particularly those with a history of chronic heart failure or chronically treated with beta-blockers. Hypotensive patients or patients with active ischemia are not the best candidates for levosimendan administration and should have these problems addressed first.

Acute heart failure (AHF) syndromes are defined as gradual or rapid change in signs and symptoms of heart failure (HF) requiring urgent therapy[1]. This is the most common reason for hospital admission among patients above 65 years of age[2]. HF hospitalizations continue to increase each year and account for 75% of hospital costs[3]. HF incidence continues to increase because of several therapeutic advances in the management of acute myocardial infarction (AMI), which are leading to improved survival in patients with impaired cardiac function, and also due to an increasingly aging population.

These syndromes are heterogeneous, encompassing an entire spectrum of patients where symptoms may be predominantly congestive, or in more advanced disease, related to low cardiac output (CO).

The past decade witnessed an increased interest in AHF because the need for early intervention and patient stabilization was recognized to improve symptoms; restore oxygenation and organ perfusion; avoid or limit cardiac, renal and other organ damage; and initiate long-term therapies that may improve outcome[4].

Unfortunately, in the absence of knowledge about causes of AHF that may benefit from specific treatment, improving patient survival has been difficult, and AHF continues to carry an ominous prognosis. This is particularly true for AHF with low CO, where low systolic blood pressure at admission has been shown to be a major outcome determinant[5,6] and where mortality is above 20% at 6 months.[5,7]

HF patients with normal or low systolic blood pressure usually have a lower left ventricular ejection fraction and frequent signs of organ hypoperfusion. These patients, who often present with hyponatremia, low peripheral temperature, renal failure, and vasodilator intolerance, are more likely to receive inotropes for lack of an alternative therapeutic option, and have the highest in-hospital mortality rate among AHF patients. Usual inotropes or inodilators like beta-adrenergic agonists and phosphodiesterase (PDE) inhibitors acutely lower filling pressures and enhance CO, improving hemodynamics and symptoms. According to an increasing number of reports in the literature[8-10], these agents, however, have been consistently associated with a detrimental effect on survival rates, regardless of the dosage used. They exert a positive inotropic action primarily by increasing cyclic adenosine monophosphate (cAMP) and intracellular calcium concentration in cardiac myocytes, but in severe HF their use may be limited by heart rate increase, arrhythmia stimulation, and by a reduced effect due to beta-adrenergic desensitization.

Given the limitations of high-dose diuretic and vasodilator use in these patients, several new pharmacologic and nonpharmacologic interventions have been introduced, while others are under development or in preclinical investigation for treatment of pulmonary and systemic congestion and restoration of CO in the setting of AHF[11].

Among these, levosimendan, the most studied calcium sensitizer, introduced in several countries for treatment of acutely decompensated HF, has both inotropic and vasodilatory effects. It differs from classic inodilators because of

Key words

Levosimendan, inotropes, inodilators, acute heart failure therapy.

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its ability to improve myocardial efficiency without increasing myocardial oxygen demand, its antistunning properties, its effects on coronary blood flow, and its lack of negative lusitropic effects[12]. Several studies have shown significant benefit in decreasing congestion, improving CO, and clinical outcome, although a recent large trial failed to confirm long-term survival benefit. The European Society of Cardiology indicates the use of levosimendan in AHF patients to treat symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction without severe hypotension[13].

In this paper, we intend to review its use in several clinical scenarios of acute heart failure.

Pharmacology and Mechanism of Action

Its chemical name is [(*R*)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl] hydrazono] propanedinitrile]. The drug is a levo-isomer of racemic simendan, a pyridazinone-dinitrile derivative. Simendan is a racemic compound made of 2 enantiomers: dextrosimendan and levosimendan.

Levosimendan belongs to the so-called group of "calcium sensitizers" that includes several other substances that share the ability of increasing sensitivity of myofilaments to calcium, leading to increased myocardial contraction without increasing intracellular cyclic adenosine monophosphate or intracellular calcium concentration, possibly with some PDE inhibitory effects. This concept seems to be associated with fewer adverse effects, lower arrhythmogenic potential, and a favorable effect on myocardial oxygen consumption compared with traditional inotropes or inodilators.

Levosimendan displays calcium-dependent binding to the N-terminal domain of cardiac troponin C (TnC) with a higher affinity at high calcium concentrations and a lower affinity at low calcium concentrations[14]. By stabilizing the calcium-TnC complex, levosimendan inhibits the troponin I (TnI) effect and prolongs the actin-myosin cross-bridge association rate. This positive inotropic effect is obtained without increasing intracellular calcium concentration or with a significant increase in myocardial oxygen demand, usually seen with other inotropes[15-17].

Beneficial effects of levosimendan are also related to its vasodilatory effects of systemic[18,19], coronary[20-22], pulmonary[23], renal[19], splanchnic[19], and cerebral arteries[19], and of systemic[18,24,25] and portal veins.[26] This effect is mediated by an adenosine tri-phosphate- (ATP) dependent potassium channel-opening effect in an ATP-dependent manner in arterial smooth muscle cells[27] of the small-resistance arteries and by a calcium-activated potassium and voltage-dependent potassium channel-opening effect in large conductance vessels[28,29]. Membrane hyperpolarization induced by the open potassium channels inhibits calcium entry and activates sodium-calcium exchange, decreasing intracellular calcium and inducing vasodilatation.

This induced decrease in right and left ventricular afterload seems to be beneficial in failing hearts[30,31].

Levosimendan has about a 1.3-hour half-life[32]. The drug is metabolized by the liver and has 2 active metabolites, OR-1855 and OR-1896, with a long half-life, 75-78 hours, which are excreted by the kidney and prolong the duration of the hemodynamic effects of their parent compound[32,33]. This long half-life is markedly increased in patients with severe chronic renal failure or end-stage renal disease who are undergoing hemodialysis as compared with healthy subjects[34].

Clinical Studies

Acute Heart Failure

Several clinical trials have shown the beneficial effect of levosimendan on short-term hemodynamic and clinical signs in patients with AHF. Kivikko et al reported[35] a 40% increase in CO and 30% decrease in pulmonary capillary wedge pressure (PCWP) after 24-hour infusion in class III-IV HF patients. The Levosimendan Infusion versus DObutamine (LIDO) study enrolled 203 patients with severe low-output HF and compared the effects of levosimendan with those of dobutamine in a double-blind fashion over 24 hours[36]. The primary end point of hemodynamic improvement (an increase of 30% or more in CO, and a decrease of 25% or more in PCWP) was achieved by 28% of the levosimendan patients and 15% of the dobutamine patients ($p = 0.022$). Interestingly, a subgroup analysis demonstrated that the use of beta-blockers enhanced the hemodynamic effects of levosimendan but reduced the hemodynamic effects of dobutamine. In this study, levosimendan treatment was also associated with a significant decrease in mortality.[37] At 31 days, all-cause mortality was significantly lower with levosimendan compared with dobutamine [hazard ratio 0.43 (95% CI 0.18-1.00) $p=0.049$]. The patients were also followed retrospectively for 180 days, and this analysis revealed that 26% of the levosimendan patients had died compared with 38% in the dobutamine group [hazard ratio 0.57 (95% CI 0.34-0.95) $p = 0.029$].

Importantly, the inodilatory effects of levosimendan were accentuated by concomitant use of beta-blocking agents in the LIDO study. In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial, levosimendan significantly improved a composite of clinical signs and symptoms of acute decompensated HF over 5 days as assessed by patients and their physicians[7]. In the Survival Of Patients With Acute Heart Failure In Need Of Intravenous Inotropic Support (SURVIVE) study, a statistically significant difference was seen early during the first 5 days, especially in patients chronically treated with a beta-blocker, but it was not evident in 180-day survival[7].

In advanced chronic HF patients awaiting cardiac transplantation, levosimendan improves renal function during the 3 months that follow drug administration.[38]

After Percutaneous Coronary Intervention or after Coronary Artery Bypass Grafting

Levosimendan improves coronary blood flow,[20,39-46] decreases myocardial oxygen extraction,[20] and improves ischemic myocardium performance[20,39,40, 42-46]. This was first shown in animals[39-41,46] and healthy humans[20] but was later shown in patients with congestive HF,[17] AMI,[43] and after percutaneous coronary intervention (PCI) of AMI patients

with LV dysfunction,[42] improving the left ventricular diastolic function of stunned myocardium in these patients[47].

In patients undergoing elective coronary artery bypass grafting (CABG), levosimendan increases CO and stroke volume and decreases systemic vascular resistance without increasing myocardial oxygen consumption or causing myocardial substrate utilization to deteriorate[44].

Diastolic Heart Failure

In animal and human preclinical studies, levosimendan has been shown to improve diastolic function, and its inotropic effect is associated with an increased rate of relaxation and reduced relaxation time, thus improving diastolic filling[48-51].

In severe HF patients with restrictive left ventricular filling assessed both by pulsed-wave Doppler echocardiography of the mitral flow and simultaneous pulmonary artery catheterization, levosimendan improved both systolic and diastolic function increasing left ventricular filling, stroke volume (-24% ± 9) and CO (29% ± 14) while decreasing PCWP (-29% ± 6). The percentage changes of the early/late transmitral diastolic peak flow velocity (E/A) ratio and the percentage changes of the isovolumetric relaxation time were independent predictors of the increase in CO in this series[52].

Peripartum Cardiomyopathy

Using new drugs in patients with rare diseases is always difficult, and only a few anecdotal reports are available describing the successful use of levosimendan in peripartum cardiomyopathy patients[53-55]. AHF is a life-threatening event that rarely occurs during or after childbirth. In these published reports, in patients with a severe episode of AHF, levosimendan improved cardiac performance that was associated both with symptomatic relief and hemodynamic or echocardiographic improvement in ventricular function. Levosimendan induced a steady decline of increased PCWP, followed by a definitive increase in cardiac stroke volume and patient recovery.

Right Heart Failure and Cardiogenic Shock

Levosimendan has also been used to restore right or left ventricular function in patients after cardiac surgery[56] and in unresponsive cardiogenic shock patients after heart transplantation primary graft failure[57,58].

In patients with low-output syndrome during or after open-heart surgery, although levosimendan use improves the hemodynamic and functional status of both groups of patients, it may be associated with increased survival and shorter ICU and hospital stay if started early, in the operating theater, instead of later, when patients are dependent on classical inotropic support and IABP[59].

In patients with acute respiratory distress syndrome (ARDS), pulmonary hypertension and right ventricular dysfunction have been associated with poor outcomes.[60-62] In a prospective, randomized, placebo-controlled, pilot study, of septic shock patients requiring mechanical respiratory support due to ARDS, levosimendan was shown to decrease mean pulmonary artery pressure, pulmonary vascular resistance index and right ventricular end-systolic volume, increasing CO, right ventricular ejection fraction, and mixed venous oxygen saturation[30].

Therapeutic Use

Treatment with levosimendan is usually initiated with a 10 minute loading bolus of 3 to 6 mcg/kg followed by a 24-hour continuous infusion of 0.05 to 0.2 mcg/kg per min. If the patient has hypotension, one should either skip the loading dose or associate norepinephrine in low doses. If there are signs of volume responsiveness, cautious fluid administration under adequate monitoring should be considered. Most patients show improvement in hemodynamic function during the next 24 hours, usually heralded by a marked increase in urinary output and a significant decrease in PCWP. This diuretic effect is often the cause of electrolyte imbalance that has been associated with arrhythmia. Pre-emptive magnesium and potassium administration should be considered to prevent hypokalemia and arrhythmia unless there is a contraindication such as renal failure.

As a powerful vasodilator, levosimendan may be a harmful drug. Although this drug exerts little influence on myocardial oxygen demand per se, in patients with active ischemia or obstructive coronary artery disease, levosimendan induced hypotension, especially in the hypovolemic patient, may precipitate tachycardia, aggravate ischemia, and increase myocardial damage, worsening long-term prognosis. Hypotensive patients or patients with active ischemia are not the best candidates for levosimendan administration and should have these problems addressed first.

References

1. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Diagnosis and treatment of acute heart failure. Guidelines of the European Society of Cardiology. Kardiol Pol. 2005; 63: 143-86.
2. Rich MW, Management of heart failure in the elderly. Heart Fail Rev. 2002; 7 (1): 89-97.
3. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006; 113: e85-151.
4. Mebazaa A, Gheorghiade M, Piña I, Harjola VP, Hollenberg S, Follath F, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Crit Care Med. 2008; in press.
5. Zannad F, Mebazaa A, Juilliere Y, Cohen-Solal A, Guize L, Alla F, et al. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: The EFICA study. Eur J Heart Fail. 2006; 8: 697-705.
6. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006; 296: 2217-26.
7. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail. 2006; 8: 105-10.
8. Cuffe MS, Califf RM, Adams KF, Bourge RC, Colucci W, Massie B, et al. Rationale and design of the OPTIME CHF trial: outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure. Am Heart J. 2000; 139: 15-22.
9. Cuffe MS, Califf RM, Adams KF Jr., Benza R, Bourge R, Colucci WS, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002; 287: 1541-7.
10. Shin DD, Brandimarte F, De Luca L, Sabbah HN, Fonarow GC, Filippatos G, et al. Review of current and investigational pharmacologic agents for acute heart failure syndromes. Am J Cardiol. 2007; 99: S4-S23.
11. Tavares M, Rezlan E, Vostroknoutova I, Khouadja H, Mebazaa A. New pharmacologic therapies for acute heart failure. Crit Care Med. in press.
12. Toller WG, Stranz C. Levosimendan, a new inotropic and vasodilator agent. Anesthesiology. 2006; 104: 556-69.
13. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J. 2005; 26: 384-416.
14. Kass DA, Solaro RJ. Mechanisms and use of calcium-sensitizing agents in the failing heart. Circulation. 2006; 113: 305-15.
15. Hasenfuss G, Pieske B, Castell M, Kretschmann B, Maier LS, Just H. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. Circulation. 1998; 98: 2141-7.
16. Ukkonen H, Saraste M, Akkila J, Knuuti MJ, Lehikoinen P, Nagren K, et al. Myocardial efficiency during calcium sensitization with levosimendan: a noninvasive study with positron emission tomography and echocardiography in healthy volunteers. Clin Pharmacol Ther. 1997; 61: 596-607.
17. Ukkonen H, Saraste M, Akkila J, Knuuti J, Karanko M, Iida H, et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther. 2000; 68: 522-31.
18. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation. 2000; 102: 2222-7.
19. Pagel PS, Hettrick DA, Warltier DC. Influence of levosimendan, pimobendan, and milrinone on the regional distribution of cardiac output in anaesthetized dogs. Br J Pharmacol. 1996; 119: 609-15.
20. Michaels AD, McKeown B, Kostal M, Vakharia KT, Jordan MV, Gerber IL, et al. Effects of intravenous levosimendan on human coronary vasomotor regulation, left ventricular wall stress, and myocardial oxygen uptake. Circulation. 2005; 111: 1504-9.
21. Kaheinen P, Pollesello P, Levijoki J, Haikala H. Levosimendan increases diastolic coronary flow in isolated guinea-pig heart by opening ATP-sensitive potassium channels. J Cardiovasc Pharmacol. 2001; 37: 367-74.
22. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, Bang L, Olesen SP, Aldershvile J. Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-sensitizing properties. J Cardiovasc Pharmacol. 1998; 31: 741-9.
23. De Witt BJ, Ibrahim IN, Bayer E, Fields AM, Richards TA, Banister RE, et al. An analysis of responses to levosimendan in the pulmonary vascular bed of the cat. Anesth Analg. 2002; 94: 1427-33.
24. Hohn J, Pataricza J, Petri A, Toth GK, Balogh A, Varro A, et al. Levosimendan interacts with potassium channel blockers in human saphenous veins. Basic Clin Pharmacol Toxicol. 2004; 94: 271-3.
25. Pagel PS, Hettrick DA, Warltier DC. Comparison of the effects of levosimendan, pimobendan, and milrinone on canine left ventricular-arterial coupling and mechanical efficiency. Basic Res Cardiol. 1996; 91: 296-307.
26. Pataricza J, Hohn J, Petri A, Balogh A, Papp JG. Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein. J Pharm Pharmacol. 2000; 52: 213-7.
27. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. Levosimendan, a novel Ca2+ sensitizer, activates the glibenclamide-sensitive K+ channel in rat arterial myocytes. Eur J Pharmacol. 1997; 333: 249-59.
28. Pataricza J, Krassoi I, Hohn J, Kun A, Papp JG. Functional role of potassium channels in the vasodilating mechanism of levosimendan in porcine isolated coronary artery. Cardiovasc Drugs Ther. 2003; 17: 115-21.
29. Yokoshiki H, Sperelakis N. Vasodilating mechanisms of levosimendan. Cardiovasc Drugs Ther. 2003; 17: 111-3.
30. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med. 2006; 34: 2287-93.
31. Kerbaul F, Rondelet B, Demester JP, Fesler P, Huez S, Naeije R, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. Crit Care Med. 2006; 34: 2814-9.
32. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikainen PJ. Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with severe heart failure. Int J Clin Pharmacol Ther. 2002; 40: 465-71.
33. Lehtonen L, Poder P. The utility of levosimendan in the treatment of heart failure. Ann Med. 2007; 39: 2-17.
34. Puttonen J, Kantele S, Kivikko M, Hakkinen S, Harjola VP, Koskinen P, et al. Effect of severe renal failure and haemodialysis on the pharmacokinetics of levosimendan and its metabolites. Clin Pharmacokinet. 2007; 46: 235-46.
35. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation. 2003; 107: 81-6.
36. Follath F, Candinas R, Meyer B. Drug therapy in supraventricular arrhythmia. Schweiz Rundsch Med Prax. 1992; 81: 579-81.
37. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002; 360: 196-202.
38. Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Card Fail. 2007; 13: 417-21.
39. Tassani P, Schad H, Heimisch W, Bernhard-Abt A, Ettner U, Mendler N, et al. Effect of the calcium sensitizer levosimendan on the performance of ischaemic myocardium in anaesthetised pigs. Cardiovasc Drugs Ther. 2002; 16: 435-41.
40. Jamali IN, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Intracoronary levosimendan enhances contractile function of stunned myocardium. Anesth

Analg. 1997; 85: 23-9.

41. Grossini E, Caimmi PP, Molinari C, Teodori G, Vacca G. Hemodynamic effect of intracoronary administration of levosimendan in the anesthetized pig. J Cardiovasc Pharmacol. 2005; 46: 333-42.

42. De Luca L, Proietti P, Celotto A, Bucciarelli-Ducci C, Benedetti G, Di Roma A, et al. Levosimendan improves hemodynamics and coronary flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction and left ventricular dysfunction. Am Heart J. 2005; 150: 563-8.

43. Kersten JR, Montgomery MW, Pagel PS, Warltier DC. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K(ATP) channels. Anesth Analg. 2000; 90: 5-11.

44. Lilleberg J, Nieminen MS, Akkila J, Heikkila L, Kuitunen A, Lehtonen L, et al. Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J. 1998; 19: 660-8.

45. Harkin CP, Pagel PS, Tessmer JP, Warltier DC. Systemic and coronary hemodynamic actions and left ventricular functional effects of levosimendan in conscious dogs. J Cardiovasc Pharmacol. 1995; 26: 179-88.

46. du Toit E, Hofmann D, McCarthy J, Pineda C. Effect of levosimendan on myocardial contractility, coronary and peripheral blood flow, and arrhythmias during coronary artery ligation and reperfusion in the in vivo pig model. Heart. 2001; 86: 81-7.

47. De Luca L, Sardella G, Proietti P, Battagliese A, Benedetti G, Di Roma A, et al. Effects of levosimendan on left ventricular diastolic function after primary angioplasty for acute anterior myocardial infarction: a Doppler echocardiographic study. J Am Soc Echocardiogr. 2006; 19: 172-7.

48. Barraud D, Faivre V, Damy T, Welschbillig S, Gayat E, Heymes C, et al. Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide-treated rabbits: comparison with dobutamine and milrinone. Crit Care Med. 2007; 35: 1376-82.

49. Tachibana H, Cheng HJ, Ukai T, Igawa A, Zhang ZS, Little WC, et al. Levosimendan improves LV systolic and diastolic performance at rest and during exercise after heart failure. Am J Physiol Heart Circ Physiol. 2005; 288: H914-922.

50. Hasenfuss G, Pieske B, Kretschmann B, Holubarsch C, Alpert NR, Just H. Effects of calcium sensitizers on intracellular calcium handling and myocardial energetics. J Cardiovasc Pharmacol. 1995; 26 (Suppl 1): S45-51.

51. Givertz MM, Andreou C, Conrad CH, Colucci WS. Direct myocardial effects of levosimendan in humans with left ventricular dysfunction: alteration of force-frequency and relaxation-frequency relationships. Circulation. 2007; 115: 1218-24.

52. Dernellis J, Panaretou M. Effects of levosimendan on restrictive left ventricular filling in severe heart failure: a combined hemodynamic and Doppler echocardiographic study. Chest. 2005; 128: 2633-9.

53. Benlolo S, Lefoll C, Katchatouryan V, Payen D, Mebazaa A. Successful use of levosimendan in a patient with peripartum cardiomyopathy. Anesth Analg. 2004; 98: 822-4.

54. Benezet-Mazuecos J, de la Hera J. Peripartum cardiomyopathy: A new successful setting for levosimendan. Int J Cardiol. 2007; in press.

55. Nguyen HD, McKeown B. Levosimendan for post-partum cardiomyopathy. Crit Care Resusc. 2005; 7: 107-10.

56. De Luca L, Colucci WS, Nieminen MS, Massie BM, Gheorghiade M. Evidence-based use of levosimendan in different clinical settings. Eur Heart J. 2006; 27: 1908-20.

57. Mebazaa A, Karpati P, Renaud E, Algotsson L. Acute right ventricular failure--from pathophysiology to new treatments. Intensive Care Med. 2004; 30: 185-96.

58. Petaja LM, Sipponen JT, Hammainen PJ, Eriksson HI, Salmenpera MT, Suojaranta-Ylinen RT. Levosimendan reversing low output syndrome after heart transplantation. Ann Thorac Surg. 2006; 82: 1529-31.

59. Tasouli A, Papadopoulos K, Antoniou T, Kriaras I, Stavridis G, Degiannis D, et al. Efficacy and safety of perioperative infusion of levosimendan in patients with compromised cardiac function undergoing open-heart surgery: importance of early use. Eur J Cardiothorac Surg. 2007; 32: 629-33.

60. Villar J, Blazquez MA, Lubillo S, Quintana J, Manzano JL. Pulmonary hypertension in acute respiratory failure. Crit Care Med. 1989; 17: 523-6.

61. Monchi M, Bellenfant F, Cariou A, Joly LM, Thebert D, Laurent I, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. Am J Respir Crit Care Med. 1998; 158: 1076-81.

62. Squara P, Dhainaut JF, Artigas A, Carlet J. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. Intensive Care Med. 1998; 24: 1018-28.

63. Follath F, Franco F, Cardoso JS. European experience on the practical use of levosimendan in patients with acute heart failure syndromes. Am J Cardiol. 2005; 96: 80G-85G.