INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

ACUTE IMPROVEMENT IN HEMODYNAMICS BY LEVOSIMENDAN IN HEART FAILURE PATIENTS IN COMPARISON WITH DOBUTAMINE

Patel Tirtha V*., Sharma KH. and Shah Jigna S.

A/1, Shaum Appartment, B/H Rajasthan Hospital, Shahibaug, Ahmedabad-380004, Gujarat, India.

ABSTRACT

The main Objective is to study hemodynamic effects of Levosimendan compare to Dobutamine on heart function in patients suffering from heart failure. A non randomized, single centre study involving 31 hospitalized patients with heart failure was conducted. 14 patients were allocated to Levosimendan group and 17 patients were allocated to Dobutamine group. The loading dose of Levosimendan was 24 µg/kg over 10 minutes followed by a continuous infusion of 0.1-0.2 µg/kg/min for 24 hours. The dose of Dobutamine was 5-10 µg/kg/min for 24 hours. The improvements in hemodynamics were checked between 24 to 72 hours after infusion of drug. Levosimendan significantly increased stroke volume, cardiac output and cardiac index by 27%, 33% and 32% respectively which was higher compared to the Dobutamine where it was 19%, 23% and 24% respectively. According to physician's assessment, a greater proportion of patients in the Levosimendan group (71%) were reported to have an improvement in dyspnea symptoms compared to Dobutamine group (64%). Levosimendan and Dobutamine increased heart rate by 3% and 4% respectively and Systolic blood pressure was decreased in Levosimendan group by 1% while it was increased by 4% in Dobutamine group. Levosimendan and Dobutamine both the drugs decreased diastolic blood pressure by 5% and 3% respectively. 24-h constant infusion of Levosimendan is superior to Dobutamine in terms of hemodynamic improvement in patients with heart failure. These hemodynamic effects appeared to be accompanied by symptom improvement and were not associated with a significant increase in the number of adverse event.

Keywords: Levosimendan, Dobutamine, Heart Failure, Hemodynamic Improvement.

INTRODUCTION

Heart failure is a clinical syndrome that can result from any disorder that impairs the ability of the ventricle to fill with or eject blood, thus rendering the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body.[1]

Unlike most other cardiovascular diseases, the prevalence of heart failure is increasing and is expected to continue to increase over the next few decades as the population ages.[2]

Acute Decompensated Heart failure (ADHF) remains a common cause of hospitalization worldwide but it is not clear how patients admitted for clinical deterioration should be managed. Patients are generally treated with diuretics and vasodilators, while patients with evidence of peripheral hypoperfusion also may receive positive inotropes, usually Dobutamine or milrinone. These positive inotropic agents improve hemodynamics and symptoms by increasing intracellular cyclic adenosine monophosphate within the failing heart but have been associated with an increased risk of death and other cardiovascular events.[3, 4]

Levosimendan is a calcium sensitizer inotropic and vasodilatory actions used in the management of acutely decompensated congestive heart failure.[5] Levosimendan is a novel drug that improves myocardial contractility by sensitizing troponin C to calcium without increasing myocardial oxygen demand.[6, 7] Levosimendan increases the sensitivity of the heart to calcium, thus

increasing cardiac contractility without a rise in intracellular calcium. Levosimendan exerts its effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner. It also has a vasodilatory effect, by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle to cause smooth muscle relaxation. Its alternative mechanisms of action to those of other traditional inotropes provide a new approach in the management of decompensated heart failure.[8, 9]

Compared with Dobutamine-treated patients, Levosimendan- treated patients have marked decreases in B-type natriuretic peptide (BNP) level and also show more favourable hemodynamic improvement in decompensated heart failure (DHF).[10, 11]

The aim of the present study was to study the hemodynamic effects of Levosimendan compare to Dobutamine on heart function in patients suffering from heart failure.

Methods

A prospective non-randomized, open-label, single centric study was chosen. All patients were evaluated echocardiographically and biochemically at baseline and between 24 h-72 h after the drug treatment. Informed consent was obtained from each patient and the study was reviewed and approved by the independent ethics committee of Sanjivani Hospital, Ahmedabad.

Thirty-one hospitalised patients with a documented LV ejection fraction of 35% or lower, and having symptoms of heart failure were enrolled. Exclusion criteria were age younger than 18 years, Significant mitral or aortic valvular stenosis, Restrictive or hypertrophic cardiomyopathy, Sustained ventricular tachycardia or ventricular fibrillation, Atrioventricular block of second or third degree, Severe renal failure (creatinine clearance below 30 ml/min), Hepatic failure, Severe angina pectoris during the 6 hours before screening, Administration of Levosimendan within 1 month before screening, Acute bleeding or severe anaemia, Heart rate persistently 130 bpm or greater at screening, Septicaemia or septic shock, Other serious diseases limiting life expectancy considerably (e.g. end-stage cancer), Participation in a clinical trial with any experimental treatment within 30 days prior to screening or previous participation in the present study and Serum potassium less than 3.5 mmol/l at screening.

Levosimendan was given as a loading dose of 24 µg/kg over 10 minutes followed by a continuous infusion of 0.1-0.2 µg/kg/min) for 24 hours. A Dobutamine infusion of 5-10 µg/kg/min was administered without a loading dose for 24 h. Primary outcome measures were Cardiac output, Cardiac index, Creatinine level, Patient's evaluation of change in dyspnea at 24 hours and Secondary outcome measures were Heart rate, Blood pressure, Adverse effects of Levosimendan and Dobutamine (like hypotension, headache, arrhythmia, tachycardia), Cardiovascular mortality during hospitalization.

The stroke volume was obtained from the echocardiographic method. Cardiac Output and Cardiac Index was calculated by the using the value of Stroke Volume.

Cardiac output (CO) was calculated using formula[12, 13]

CO = Stroke Volume X Heart Rate

Cardiac Index (CI) was calculated using formula[14, 15]

CI = Cardiac Output/Body Surface Area

Statistical analysis

Results were presented as mean ± SD for continuous variables and as a percentage of total for categorical variables. Mean values of continuous variables were compared between groups using the Student's *t* test, according to whether variables were normally or non-normally distributed. Similarly, the paired *t* test was used, to compare mean values before and after treatments. $P<0.05$ was considered to be statistically significant. Software used for the analysis was GraphPad Prism 5.

RESULTS

Patient enrolment was from January-2012 until April-2012. There was no significant difference in demographics of patients (Table 1).

The two study groups were well balanced with respect to baseline characteristics (Table 2). No significant differences in stroke volume, ejection fraction, cardiac output, cardiac index, serum Creatinine, heart rate, systolic or diastolic blood pressure responses were encountered between the two treatment arms. All patients completed the study.

Efficacy

Hemodynamic assessment

Both Levosimendan and Dobutamine infusion induced hemodynamic improvement (Table 3). The Stroke volume and ejection fraction were increased in both the Levosimendan and Dobutamine group, although the increase in Stroke volume was significantly greater in Levosimendan group [$P<0.001$]. The mean Cardiac Output and Cardiac Index increased in

both the Levosimendan and Dobutamine groups, although the improvement in Cardiac output and cardiac index were greater in the Levosimendan group (33 % versus 23 % and 32 % versus 24 %, respectively) (Table 4). There was no marked change in Serum Creatinine level in both the groups.

Symptomatic improvement

According to investigator's assessment of dyspnea, the difference between the groups after drug administration was statistically significant; 71 % of patient in the Levosimendan group verses 64 % in the Dobutamine group were reported to have improvement in Dyspnea.

Safety and Tolerability

Systolic blood pressure initially declined in the Levosimendan group and increased in Dobutamine group while Diastolic Blood Pressure is more declined in Levosimendan group than in the Dobutamine group (Table 3). Heart rate increased more in the Dobutamine group than in the Levosimendan group (Table 4).

The Adverse Event profiles were generally similar in both treatment groups (Table 5) with the exception of tachycardia, which was more frequent in Dobutamine group (58.82% versus 35.71 %). Compared with Dobutamine-treated patients, Levosimendan-treated patients were more likely to experience Headache (35.71% versus 5.88%). The treatment groups were similar with respect to frequency of hypotension and arrhythmias. No death was occurred in any of the groups.

DISCUSSION

This open label, single centric study was designed to compare the improvement in hemodynamics after infusion of Levosimendan and Dobutamine in the hospitalised patients having heart failure. The study indicated that a 24-h constant infusion of the new calcium sensitizer Levosimendan is superior to the commonly used beta-agonist Dobutamine in terms of hemodynamic improvement in patients with heart failure. This was consistent with the previous findings in the LIDO study.

In the LIDO trial (Levosimendan Infusion vs. Dobutamine), patients hospitalized for an acute decompensation of CHF were treated with infusions of Levosimendan or Dobutamine.[16] Results showed that haemodynamic responses among patients on b-blockers were enhanced for those treated with Levosimendan but blunted for those who received Dobutamine.[16] This was confirmed by the prospectively designed BEAT-CHF study.[17]

LIDO results further suggested a 180 day survival advantage after initial infusion of Levosimendan, in comparison with Dobutamine.[16] Results of the SURVIVE trial, specifically designed to compare mortality outcomes in patients hospitalized for acute heart failure, showed numerically fewer deaths among individuals given Levosimendan infusions compared with Dobutamine, but the differences were not statistically significant at 31 and 180 day endpoints.[10]

In our study Levosimendan significantly increased stroke volume, cardiac output and cardiac index by 27%, 33% and 32% respectively which was higher compared to the Dobutamine where it was 19%, 23% and 24% respectively. However, the difference in improvement of hemodynamic variables between the two groups was not statistically significant except stroke volume.

Levosimendan has been shown to improve both systolic and diastolic function in dogs with pacing-induced heart failure.[18] In healthy humans, Levosimendan increased SV and CI without increasing heart rate.[19] When administered as a bolus to patients shortly after coronary bypass surgery, Levosimendan increased coronary blood flow without increasing myocardial oxygen consumption.[20] In a dose-finding study performed in 24 patients with reduced LV ejection fraction, a single bolus infusion of Levosimendan at doses of 0.25 and 0.5 mg selectively increased SV, whereas higher doses increased heart rate as well.[21] Although pharmacokinetic parameters were not measured in the present study, previous studies have shown that Levosimendan has an active metabolite (OR-1896), which has a considerably longer elimination half-life than the parent drug (About 80 vs.1 h).[22, 23] This confers distinct advantage to Levosimendan over Dobutamine of prolonged hemodynamic effects, which last for up to 7-9 days.

In both the group treatment groups, the majority of patients reported either improved or unchanged dyspnea. According to physicians' assessment, a greater proportion of patients in the Levosimendan group (71%) were reported to have an improvement in dyspnea symptoms compared to Dobutamine group (64%).

Our data suggested that S.Creatinine increased insignificantly in both the treatment groups (1% in Levosimendan group as well as in Dobutamine group). So that we can say there was no significant effect of Levosimendan and Dobutamine on renal function.

According to present study Levosimendan increased heart rate by 3% and Dobutamine

increased heart rate by 4%. Similar results were reported in the LIDO and SURVIVE studies.[24]

Compared with Dobutamine-treated patients, Levosimendan-treated patients were more likely to experience an initial decrease in systolic and diastolic blood pressure.[10] In our study Systolic blood pressure was decreased in Levosimendan group by 1% while it was increased by 4% in Dobutamine group. Levosimendan and Dobutamine both the drugs decreased diastolic blood pressure by 5% and 3% respectively.

At higher concentrations, Levosimendan can inhibit phosphodiesterase III in myocardium[25] and vascular smooth muscle.[26] Thus, the safety and tolerability of Levosimendan is more as compared to Dobutamine.

Although sample size was small findings were consistent with the more frequent reporting of hypotension as an AE for Levosimendan patients (35%), SBP decreased more during the infusion of Levosimendan than Dobutamine.[24] This is in contrast to the SURVIVE study, where a similar proportion of patients experienced hypotension as an AE (16% for Levosimendan and 14% for Dobutamine).[24]

The adverse event reported was similar in both the group but incidence of tachycardia was higher in patient treated with Dobutamine (10 patients) compared to patient treated with Levosimendan (5 patients). Among all patients 5 patients had a complain of headache who were treated with Levosimendan while in Dobutamine treated group headache incidence was observed 1 patient only. In Levosimendan group 1 patient had a hypotension. Overall no any death was reported in both the groups.

In summary, the present study demonstrates that Levosimendan causes a rapid dose-dependent improvement in hemodynamic function in patients with heart failure compared to the Dobutamine. Although the mechanism of action cannot be determined from these data, the observed hemodynamic effects are consistent with the known pharmacological actions of this drug as a calcium sensitizer and direct vasodilator. Levosimendan patients reported greater improvement in dyspnea symptoms than Dobutamine. Thus, Levosimendan may be of value in the short-term treatment of patients with heart failure. Although our results suggest that Levosimendan seems to be a better option than Dobutamine, long term studies with a larger population size and for a longer follow up duration in Indian patients are required to confirm the superiority of Levosimendan as compared to Dobutamine in Indian patients with heart failure.

Table 1: Demographic Details of the patients

Characteristics	Levosimendan (GROUP-I) N=14	Dobutamine (GROUP-II) N= 17
Male, %	09 (64.28%)	11 (64.70%)
Female, %	05 (35.71%)	06 (35.29%)
Age (years)	57.28 ± 16.97	54.70 ± 12.12
Height (cm)	166.28 ± 7.47	164.29 ± 8.28
Weight (kg)	63.5 ± 11.94	60.35 ± 9.63
BSA (m^2)	1.69 ± 0.19	1.65 ± 0.15

Data presented as mean ± SD unless otherwise indicated.

Table 2: Baseline Cardiac Parameters of the patients

Parameters	Levosimendan (GROUP-I) N=14	Dobutamine (GROUP-II) N= 17
Stroke volume (ml)	35.71 ± 2.97	35.70 ± 2.99
Ejection Fraction (%)	22.14 ± 2.56	24.70 ± 4.13
Cardiac Output (L/min)	3.41 ± 0.33	3.46 ± 0.33
Cardiac Index ($L/min/m^2$)	2.05 ± 0.26	2.08 ± 0.24
S. Creatinine (mg/dl)	1.01 ± 0.29	0.97 ± 0.26
Heart Rate (beats/min)	95.57 ± 3.43	96.23 ± 4.99
SBP (mmHg)	120.28 ± 15.20	121.35 ± 13.44
DBP (mmHg)	77 ± 10.39	77.17 ± 6.08

Values are in mean ± SD

Table 3: Cardiac Parameters of the patients before and after treatment

Variables	Levosimendan (GROUP-I) N=14		Dobutamine (GROUP-II) N= 17	
	Pre-admin.	Post-admin.	Pre-admin.	Post-admin.
Stroke volume (ml)	35.71 ± 2.97	45.64 ± 3.34*#	35.70 ± 2.99	42.58 ± 3.10*
Dyspnea	√	√ (71% population feel relief)	√	√ (64% population feel relief)
Ejection Fraction (%)	22.14 ± 2.56	25.71 ± 3.31*	24.70 ± 4.13	27.05 ± 4.69**
Cardiac Output (L/min)	3.41 ± 0.33	4.55 ± 0.40*	3.46 ± 0.33	4.28 ± 0.37*
Cardiac Index ($L/min/m^2$)	2.05 ± 0.26	2.71 ± 0.36*	2.08 ± 0.24	2.59 ± 0.35*
S. Creatinine (mg/dl)	1.01 ± 0.29	1.04 ± 0.28	0.97 ± 0.26	1.03 ± 0.32
Heart Rate (beats/min)	95.57 ± 3.43	98.35 ± 2.70*	96.23 ± 4.99	100.11 ± 4.92*
SBP (mmHg)	120.28 ± 15.20	118 ± 14.07**	121.35 ± 13.44	126.41 ± 13.06*
DBP (mmHg)	77 ± 10.39	72.42 ± 9.77*	77.17 ± 6.08	74.82 ± 5.91**

Values are in mean ± SD
*p value <0.0001 verses baseline, ** p value <0.001 verses baseline,
p value < 0.001 when compared Levosimendan post-administration with Dobutamine post-administration (by using Student's t-test).

Table 4: Change (%) in Hemodynamic Variables of the two treatment groups after Administration

Hemodynamic Variables	Levosimendan (%)	Dobutamine (%)
Stroke Volume	27	19
Ejection Fraction	16	9
Cardiac Output	33	23
Cardiac Index	32	24
S.Creatinine	1	1
Heart Rate	3	4
SBP	-1	4
DBP	-5	-3

Table 5: Adverse Events observed in the two treatment group

Adverse event	Levosimendan N=14	Dobutamine N=17
Tachycardia	05 (35.71%)	10 (58.82%)
Arrhythmia	00	00
Headache	05 (35.71%)	01 (5.88%)
Hypotension	01 (7.14%)	00
Death (SAE)	00	00

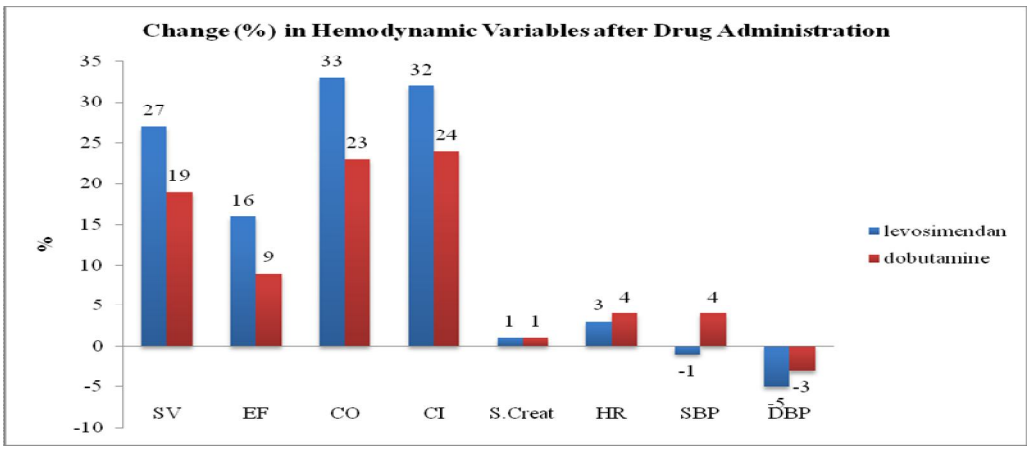

Fig. 1: Change (%) in Hemodynamic variables after Drug Administration

CONCLUSION

The present study demonstrated that Levosimendan is a better choice of drug as compared to Dobutamine, as improvement in hemodynamics i.e. cardiac output and cardiac index was observed in higher proportion of patients as compared to Dobutamine. The tachycardia was produced in both treatment groups but the incidence was higher in Dobutamine group. Our study also revealed that the Levosimendan cause greater improvement in dyspnea symptom than Dobutamine.

REFERENCES

1. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. Circulation 2001; 104: 2996–3007.
2. Parker RB, Patterson JH, Johnson JA, Heart Failure, In: Dipiro JT, Gary CY, Robert JT, Gary RM, Barbara GW, editors. Pharmacotherapy: A Pathophysiologic approach, 6th Edn, McGraw Hill companies, USA, 2005. pp. 219-260.
3. Cuffe MS, Califf RM, Adams KF Jr, et al. Shortterm intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002; 287: 1541-1547.
4. Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. Am J Cardiol. 2005; 96(6A): 47G-58G.
5. AA, MK, PR, Simdex (Levosimendan), Simdax Fact Sheet, Orion Pharma, 6 May 2009.
6. Figgit DP, Gillies PS, Goa KL. Levosimendan. Drugs 2001;61:613-27
7. Innes CA, Wagstaff AJ. Levosimendan: A review of its use in the management of acute decompensated heart failure. Drugs 2003;63:2651-71
8. Cavusoglu Y., The use of levosimendan in comparison and in combination with dobutamine in the treatment of decompensated heart failure. Expert Opinion on Pharmacotherapy 2007 Apr; 8(5): 665-77.
9. Levosimendan, http://www.drugbank.ca/drugs/DB00922
10. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, Padley RJ, Huang B, and Solal AC, Levosimendan verses Dobutamine for Patients With Acute Decompensated Heart Failure-The SURVIVE Randomized Trial, JAMA, May 2, 2007—Vol 297, No. 17 1883-1891.
11. Nanas JN, Papazoglou PP, Terrovitis JV, et al. Hemodynamic effects of Levosimendan added to Dobutamine in patients with decompensated advanced heart failure refractory to Dobutamine alone. Am J Cardiol 2004; 96:1329-32.
12. Lavdaniti M., Invasive and non-invasive methods for cardiac output measurement, Vol 1 Issue 3, Sept - Dec 2008.
13. Cardiac Output calculation, http://www.easycalculation.com/medical/fick.php
14. Cardiac Index measurement, http://www.livestrong.com/article/188133-cardiac-indexmeasurement/#ixzz1gyPYb5Yh
15. Fick Cardiac Output Calculator, http://www.josephsunny.com/medsoft/cardiology.html
16. Follath F, Cleland J, Just H, Papp J, Scholz H, Peuhkurinen K, Harjola V, Mitrovic V, Abdall M, Sandell E-P, Lehtonen L. Efficacy and safety of intravenous levosimendan, a novel calcium sensitiser, in severe low output failure (the LIDO study): a randomised double-blind trial. Lancet 2002; 360: 196–202.
17. Bergh C-H, Dahlstrom U, Forfang K, Kivikko M, Sarapohja T, Ullman B, Wikstrom G. Intravenous levosimendan versus dobutamine in acute decompensated heart failure patients treated with beta-blockers (BEAT-CHF study). Eur Heart J 2007; 28: S388–S389, no. 2444.
18. Pagel PS, McGough MF, Hettrick DA, et al. Levosimendan enhances left ventricular systolic and diastolic function in conscious dogs with

pacinginduced cardiomyopathy, J Cardiovasc Pharmacol. 1997; 29: 563–573.
19. Sundberg S, Lilleberg J, Nieminen MS, et al. Hemodynamic and neurohumoral effects of levosimendan, a new calcium sensitizer, at rest and during exercise in healthy men. Am J Cardiol. 1995; 75: 1061–1066.
20. Lilleberg J, Nieminen MS, Akkila J, 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: 660–668.
21. Lilleberg J, Sundberg S, Nieminen MS. Dose-range study of a new calcium sensitizer, levosimendan, in patients with left ventricular dysfunction, J Cardiovasc Pharmacol. 1995; 26 (suppl 1):S63–S69.
22. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikainen PJ. Pharmacokinetics of Levosimendan and its metabolites during and after a 24 h continuous infusion in patients with severe heart failure. Int J Clin Pharmacol Ther 2002; 40: 465–471.
23. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003; 107: 81–86.
24. Bergh CH, Andersson B, Dahlstro UM, Forfang K, Kivikko M, Sarapohja T, Ullman B, and Wikstro GM, Intravenous Levosimendan vs. Dobutamine in acute decompensated heart failure patients on beta-blockers, European Journal of Heart Failure (2010) 12, 404–410.
25. Sato S, Talukder MA, Sugawara H, et al. Effects of Levosimendan on myocardial contractility and Ca21 transients in aequorin-loaded right-ventricular papillary muscles and indo-1-loaded single ventricular cardiomyocytes of the rabbit. J Mol Cell Cardiol. 1998; 30: 1115–1128.
26. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, et al. Coronary vasorelaxant effect of Levosimendan, a new inodilator with calcium-sensitizing properties, J Cardiovasc Pharmacol. 1998; 31: 741–749.