*Acta Anaesthesiol Scand 2003; **47:** 1251–1256*
Printed in Denmark. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
ISSN 0001-5172

Hemodynamic effects of a continuous infusion of levosimendan in critically ill patients with cardiogenic shock requiring catecholamines

G. Delle Karth, A. Buberl, A. Geppert, T. Neunteufl, M. Huelsmann, C. Kopp, M. Nikfardjam, R. Berger and G. Heinz
Department of Cardiology, University of Vienna, Vienna, Austria

Background: Levosimendan, a novel inodilator, has been shown to improve hemodynamic function in patients with decompensated heart failure with preserved arterial blood pressure. Data on its use in patients with cardiogenic shock are rare. The present series describes the 24-h hemodynamic effects of levosimendan as add-on therapy in desperately ill patients with cardiogenic shock requiring catecholamines.
Methods: Ten patients with cardiogenic shock received levosimendan as continuous infusion of $0.1\,\mu g\,kg^{-1}\,min^{-1}$ for 24 h. The patients were otherwise unselected. Hemodynamic measurements were routinely performed at baseline (time 0) and at 1, 8, 16 and 24 h after start of levosimendan (LS) using a Swan-Ganz thermodilution catheter.
Results: During the levosimendan infusion there was a significant increase in cardiac index from 1.8 ± 0.4 to 2.4 ± 0.6 $L*min^{-1}*m^{-2}$ ($P = 0.023$) and a significant decrease in systemic vascular resistance from 1559 ± 430 to 1109 ± 202 $dyn*s*cm^{-5}$ ($P = 0.001$), respectively. Changes in catecholamine dose, and in systolic and diastolic blood pressure were not significant. Given the individual response to LS, 8/10 patients showed an increase in left ventricular stroke work index under reduced or roughly unchanged preload conditions after 8 h.
Conclusion: This series shows that a LS infusion is feasible and able to improve hemodynamics in severely compromized, critically ill patients with cardiogenic shock requiring catecholamine therapy. Its potential advantages when compared with other inotropes are unclear. To clarify the potential role of LS in this clinical setting randomized controlled trials on hemodynamic and mortality endpoints are needed.

Accepted for publication 8 August 2003

Key words: Calcium; cardiogenic shock; inotropic agents; levosimendan.

Cardiogenic shock remains the leading cause of death in patients hospitalized for myocardial infarction, decompensated heart failure and in patients after cardiac surgery, with mortality rates up to 80% (1, 2). In all patients the first priority must be rapid stabilization and treatment of reversible causes, e.g. revascularization. Mechanical assist devices, inotropes and vasopressor agents have been used in the management of patients with cardiogenic shock. Various types of inodilators and vasopressors have been tested in this situation, ranging from purely inotropic and vasodilating to purely vasopressor agents (3, 4). However, the ideal pharmacological treatment is still elusive. Levosimendan (LS) is a new calcium sensitizer that exerts positive inotropic effects without increasing intracellular cAMP or Ca^{2+} at therapeutic doses (5) and therefore may avoid major limitations of β-Adrenergic agents (6). It has shown to improve hemodynamic function in patients with decompensated non-hypotensive heart failure (7–10). Two large randomized studies on patients with chronic and acute congestive heart failure did not find an increase in mortality with levosimendan. In the LIDO trial (9) there was a 52.9% survival benefit at day 31 when compared with patients receiving dobutamine. In the RUSSLAN trial (10), the survival benefit approached 40% after 14 days. In addition, levosimendan exerts antistunning effects (11), does not increase oxygen demand (12) and was successfully employed in the perioperative setting (13). In an animal study LS potentiated the positive inotropic effects of dopamine while attenuating the negative effects of dopamine on chamber compliance (14). Data on its use in patients with cardiogenic shock are rare. We report on our experience with LS as add-on therapy in severely compromized, critically

ill patients with refractory cardiogenic shock requiring catecholamine therapy.

Methods

Patients

Patients with cardiogenic shock due to acute myocardial infarction, decompensated heart failure or post cardiac surgery were considered candidates for LS administration. All patients were treated in an eight-bed medical cardiologic intensive care unit at a university hospital. Patients received LS for clinical reasons in a critical hemodynamic condition as adjunctive therapy to revascularization, intra-aortic balloon counterpulsation and catecholamines. Patients were deemed candidates for LS due to refractory cardiogenic shock if they could not be stabilized despite the above-mentioned means within 6 h. The indication for LS treatment was at the discretion of the cardiologist based on compassionate use grounds. The patients were otherwise unselected. Patients with significant (moderate to severe) aortic stenosis or mitral regurgitation were not considered candidates for LS.

A diagnosis of cardiogenic shock was made if (1) the cardiac index (CI) was <2.2 l*min^{-1}*m^{-2} in the presence of (2) a pulmonary capillary wedge pressure (PCWP) >16 mmHg, (3) there were persistent hypotension (systolic blood pressure <90 mmHg or requirement of catecholamines) and (4) clinical signs of cardiogenic shock (e.g. cold skin, mental confusion, oliguria) (15). All patients with acute myocardial infarction underwent coronary catheterization and percutaneous coronary intervention. Baseline echocardiography was available in all patients. Quantitative analysis could be performed on all echocardiograms. Left ventricular volumes were measured by the modified Simpson method.

Hemodynamic measurements

Arterial blood pressure measurements were performed using the indwelling arterial cannula inserted into the radial artery. For measurement of pulmonary artery pressure, PCWP and right atrial pressure, a 7.5-F pulmonary artery Swan-Ganz thermodilution catheter (Model 831HF75, Edwards Lifesciences, Irvine, CA) was used.

Pressure values were read from the bedside patient monitor (HP-CMS 78580; Hewlett-Packard, Andover, MA) at end-expiration. Cardiac output measurements were performed in triplicate using a closed injectate delivery cardiac output set (Model 41424-61-03; Abbott Critical Care Systems, North Chicago, IL) and 10 ml of saline at room temperature in combination with the cardiac output computer integrated into the bedside monitor (HP-CMS 78580). Standard formulas implemented in our bedside monitor system and patient data management system were applied for calculation of left ventricular stroke work index (LVSWI) and resistances. Hemodynamic measurements were routinely performed by one of us at baseline (time 0) and at 1, 8, 16 and 24 h after start of LS. Heart rate (HR) and rhythm, blood pressure and O_2 saturation were continuously monitored. Renal failure was defined as oliguria (<20 ml h^{-1}) accompanied by an increase in serum creatinine of at least 44 μmol l^{-1} greater than baseline/or severe renal dysfunction requiring extracorporal renal support.

Levosimendan treatment

Levosimendan (Orion Pharma, Helsinki FI) was administered protocol driven at the recommended standard dose for a continuous infusion as a drip of 0.1 μg*kg^{-1}*min^{-1} for 24 h. Treatment with fluids (crystalloids and colloids) was adjusted to maintain a PCWP of approximately 16 mmHg. Catecholamines were basically selected according to the ACC/AHA guidelines for the management of patients with acute myocardial infarction (16) at the discretion of the attending physician. In one patient with cardiogenic shock due to acute myocardial infarction epinephrine was used, in another patient both epinephrine and nor-epinephrine were administered. The dosage of catecholamines was adjusted to maintain a mean arterial pressure >65 mmHg.

Statistical analysis

Changes in hemodynamic variables over the study period were analyzed by one-way ANOVA followed by Tukey's tests. Mean and standard deviations are given in all analyses. A P-value <0.05 was considered significant.

Results

Ten patients with cardiogenic shock received LS as add-on therapy. Baseline characteristics are given in Table 1. Two patients with acute renal failure were treated with renal replacement therapy. Analgosedation initiated 24 ± 8 h before the LS infusion was achieved by a continuous fentanyl (4.3 ± 0.5 μg*kg^{-1}*h^{-1}) and midazolam infusion (224 ± 29 μg*kg^{-1}*h^{-1}). The dosage of analgosedation was not changed substantially during the LS infusion

Table 1

Baseline characteristics of patients at the start of the levosimendan infusion.

Parameter	
Age (years)	71.9 ± 6.1
APACHE-II score (points)	26.7 ± 10.1
Predicted mortality (%)	51.2 ± 31.1
Baseline echocardiograms	
LV end-diastolic volume (ml)	123.5 ± 29.6
LV end-systolic volume (ml)	87.9 ± 23.3
LVEF (%)	28.8 ± 5.0
Sex: Male/Female	9/1
Causes of cardiogenic shock	
Post cardiac surgery	2
Acute myocardial infarction	4
Dilated cardiomyopathy	2
HTX: late graft failure	1
Cardiac-amyloidosis (highly reduced LVF)	1
Acute renal failure	7
Mechanical ventilation	7
Analgosedation	7
Intra-aortic balloon pump	3
Nor-epinephrine infusion	7
Epinephrine infusion	1
Nor- and epinephrine infusion	1
Dobutamine infusion	1

APACHE = Acute Physiology and Chronic Health Evaluation; HTX = heart transplantation.

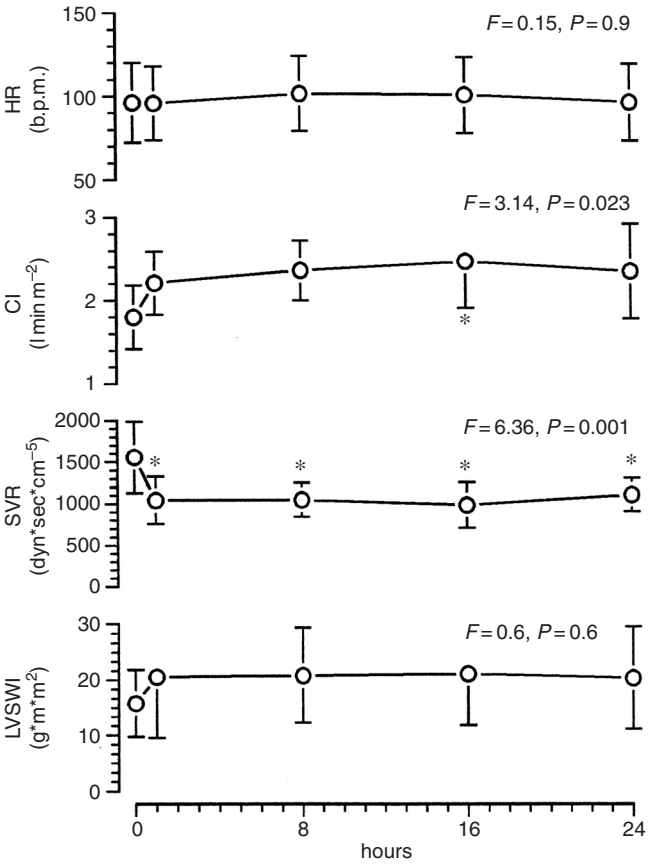

*Fig. 1. Changes in heart rate (HR), cardiac index (CI), systemic vascular resistance (SVR) and left ventricular stroke work index (LVSWI) during levosimendan (LS) treatment. *Significantly different from baseline.*

(fentanyl $3.8 \pm 0.5\,\mu g{*}kg^{-1}{*}h^{-1}$ and midazolam $226 \pm 41\,\mu g{*}kg^{-1}{*}h^{-1}$ at hour 24, respectively). In one patient with acute myocardial infarction an intra-aortic balloon pump could not be inserted due to severe peripheral artery disease. The two patients with postoperative cardiogenic shock were also treated with intra-aortic balloon counterpulsation but not at the time of the LS infusion. In 7/10 patients serum lactate levels were greater than $1.5\,mmol\,l^{-1}$ at the start of the LS infusion. Table 1 gives data on baseline echocardiograms and shows that all patients had severely reduced left ventricular function.

Levosimendan administration resulted in a significant increase in CI and a significant decrease in systemic vascular resistance (Fig. 1). A small increase in heart rate was not significant. The LVSWI did increase during the 24-h LS infusion but these changes were not significant on ANOVA. Considering the individual response to the LS infusion at 8 h, the LVSWI increased in eight patients, and remained unchanged or decreased in one patient each. The PCWP decreased in six patients, remained unchanged in one patient and slightly increased in three patients, respectively (Fig. 2). Both patients who were unable to increase their LVSWI died.

The course of other hemodynamic parameters during the study period is presented in Table 2. There was a slight but insignificant decrease in the PCWP and pulmonary vascular resistance. There was no clear trend in pulmonary arterial pressures. Systolic arterial pressure, mean arterial pressure, and diastolic arterial pressure did not change significantly during the 24-h treatment period. The subtle changes in mixed venous oxygen saturation were not significant.

To maintain arterial blood pressure greater than 65 mmHg during the LS infusion, the dose of catecholamines had to be increased in four patients while it could be reduced in five patients. On average there was no significant change in catecholamine dosage. Further, to maintain adequate filling pressures, a positive fluid balance of 2932 ± 2478 ml was required. This was achieved by a total of 3846 ± 1964 ml of crystalloids and 330 ± 505 ml of colloids in 9/10 patients, respectively. In one patient a mild negative fluid balance was achieved.

In two patients who died shortly after the end of the LS infusion from irreversible cardiogenic shock (9 and 12 h after the LS infusion, respectively, 36-h non-survivors) the doses of catecholamines had to be

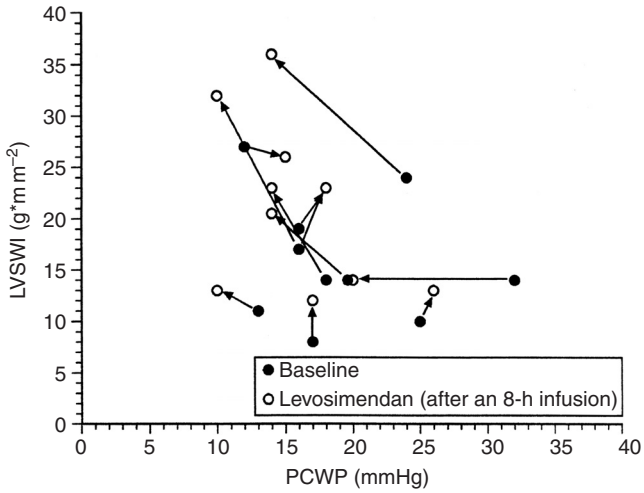

Fig. 2. Individual short-term changes in left ventricular stroke work index (LVSWI) and pulmonary capillary wedge pressure (PCWP) during a levosimendan (LS) infusion. Given are individual 8-h values during the LS infusion (●) vs. the values before the start of the LS infusion (○). Corresponding changes in PCWP are shown on the abscissa. In 8/10 patients LVSWI increased and in 7/10 patients PCWP decreased or remained unchanged after an 8-h LS administration. In one patient LVSWI deteriorated and in one patient LVSWI did not increase. In three patients PCWP increased slightly.

increased from $1.10 \pm 0.80\,\mu g*kg^{-1}*min^{-1}$ at baseline to $2.22 \pm 1.25\,\mu g*kg^{-1}*min^{-1}$ at 24 h. In seven patients (36-h survivors) only subtle adjustments in the catecholamine dose from $0.34 \pm 0.17\,\mu g*kg^{-1}*min^{-1}$ at baseline to $0.35 \pm 0.20\,\mu g*kg^{-1}*min^{-1}$ at 24 h were necessary. Changes in the catecholamine dose were not significant for the group as a whole. In one patient (36-h survivor) in whom LS was administered as add-on therapy to dobutamine, the dose of dobutamine was unchanged. Lactate levels decreased during LS therapy in eight patients and increased in two patients. Changes in lactate levels were not significant for the group as a whole ($3.6 \pm 2.4\,mmol\,l^{-1}$ at baseline to $3.5 \pm 5.2\,mmol\,l^{-1}$ at hour 24, respectively, $P = 1.0$). In the 36-h survivors lactate levels decreased from $2.7 \pm 1.4\,mmol\,l^{-1}$ at baseline to $1.6 \pm 0.83\,mmol\,l^{-1}$ at 24 h, whereas in the 36-h non-survivors lactate levels increased from $7.1 \pm 1.9\,mmol\,l^{-1}$ at baseline to $11.7 \pm 13.2\,mmol\,l^{-1}$ at 24 h, respectively.

In none of the patients had LS to be discontinued before the 24-h period. We were unable to detect any clinical adverse effect of the LS treatment. There were four survivors who could be weaned from catecholamines after LS administration and were discharged from the intensive care unit. Three patients were discharged to home; one patient received a biventricular assist device as bridging to heart transplantation after discharge to a step-down care. These latter four patients were alive at 6-month follow up. The six non-survivors died of refractory cardiogenic shock (n = 4), intracerebral bleeding (n = 1) and mesenteric embolization (n = 1), respectively.

Discussion

The present series in critically ill patients with cardiogenic shock shows that a LS infusion is feasible and able to improve hemodynamic function in this severely compromized population. The effect of LS was comparable to that previously shown in patients with chronic heart failure (7–10), and in a perioperative setting in patients with a preserved left ventricu-

Table 2

Hemodynamic parameters during the levosimendan treatment.

	Baseline	1 h	8 h	16 h	24 h	*P*-value
SAP	116.2 ± 15.0	111.5 ± 15.5	115.2 ± 16.9	107.8 ± 19.4	116.5 ± 19.9	0.769
DAP	56.6 ± 11.4	54.8 ± 10.2	62.0 ± 19.3	53.9 ± 9.8	54.9 ± 5.8	0.584
MAP	75.3 ± 8.7	72.5 ± 10.3	73.2 ± 12.4	71.2 ± 9.2	73.8 ± 7.7	0.914
Catechols	0.50 ± 0.44	0.51 ± 0.45	0.69 ± 1.03	0.66 ± 0.88	0.72 ± 0.90	0.946
RAP	12.6 ± 4.6	13.2 ± 4.7	11.8 ± 3.0	11.1 ± 3.3	13.5 ± 3.9	*
PCWP	19.3 ± 6.1	18.4 ± 8.2	15.8 ± 4.8	16.9 ± 5.5	18.9 ± 5.9	0.687
PAPs	45.0 ± 13.2	51.0 ± 15.6	44.9 ± 8.7	43.1 ± 10.1	46.0 ± 10.9	0.674
PAPd	24.4 ± 4.9	27.3 ± 7.2	27.9 ± 5.0	23.7 ± 5.5	24.4 ± 4.4	0.317
PAPm	31.5 ± 6.6	35.3 ± 8.0	33.7 ± 4.8	30.9 ± 6.3	31.7 ± 5.4	0.522
PVR	290 ± 133	288 ± 106	259 ± 78	245 ± 93	257 ± 97	0.831
$MVSO_2$	57.2 ± 9.3	58.5 ± 10.6	60.3 ± 10.2	59.5 ± 8.7	59.2 ± 6.0	0.956

SAP = systolic arterial pressure (mmHg); DAP = diastolic arterial pressure (mmHg); MAP = mean arterial pressure (mmHg); Catechols = combined dose of nor- and epinephrine ($\mu g*kg^{-1}*min^{-1}$); RAP = right atrial pressure (mmHg); PCWP = pulmonary capillary wedge pressure (mmHg); PAPs = systolic pulmonary arterial pressure (mmHg); PAPd = diastolic pulmonary arterial pressure (mmHg), PAPm = mean pulmonary arterial pressure (mmHg); PVR = pulmonary vascular resistance ($dyn*s*cm^{-5}$); $MVSO_2$ = mixed venous oxygen saturation.*Not computed; all values are given as mean ± SD.

lar function (13). Thus, our findings extend previous data on LS to a population with cardiogenic shock.

The main effect observed was an increase in CI and a decrease in systemic vascular resistance. Increases in CI might solely be explained by a consistent decrease in left ventricular afterload. However, direct inotropic effects may also be involved. Though we did not measure inotropy directly, an indication for a positive inotropic action might be the increase of LVSWI in 8/10 patients while preload conditions remained unchanged or were slightly reduced and there were only subtle changes in heart rate. The increases in LVSWI were paralleled by decreases in lactate levels, suggesting, although not significant, an improved tissue oxygenation and shock reversal. This fact supports the overall beneficial hemodynamic effects of LS in this clinical setting and shows that LS helps to revert shock even in this severely compromized population. The two patients who showed no improvement or deterioration in LVSWI and consecutively increasing lactate levels were non-survivors. The two 36-h non-survivors had probably too advanced myocardial damage and were beyond any treatment: In those two patients the lactate levels were 8.5 and 5.8 $mmol\,l^{-1}$, respectively, at the beginning of the LS infusion.

The doses of catecholamines had to be increased only moderately during the LS infusion in two of 10 patients at the dosage of LS applied. A profound increase in catecholamines was necessary in two patients that rapidly deteriorated and died within 36 h of irreversible cardiogenic shock. Most likely, the increasing catecholamine requirement was a consequence of the irreversible myocardial damage. The latter two patients had a rapidly increasing catecholamine requirement before LS and were on catecholamine doses beyond $0.5\,\mu g*kg^{-1}*min^{-1}$ when the LS infusion was started. Of course, the possibility of a LS-induced hemodynamic deterioration cannot be excluded with certainty.

We did not administer a bolus dose of LS in our severely compromized patients. This strategy comes from our previous experience with other inodilators, e.g. milrinone in a similar population (17). We do not give a milrinone bolus either in our patients, since we observed profound decreases in blood pressure. Nevertheless, a substantial increase in CI was seen in all patients after 1 h and the increase in CI was significant at 16 h for the entire group. We did not compare the vasodilating effect of LS with that of other inodilators but it is our clinical feeling that the vasodilation of LS is less pronounced in the dosage used when compared with other available inotropes. Others have used the no-bolus strategy as well (18).

The results of the present series are only a preliminary report of LS in a small number of patients with cardiogenic shock. With respect to further trials on LS in this desperately ill patient population, it has been clearly shown that a LS infusion is feasible and results in hemodynamic improvement within a short time even without a bolus dose. The patients were unselected and represent a mixture of patients with acute myocardial infarction, decompensated chronic heart disease and post cardiac surgery encountered in many intensive care or emergency department units.

Due to the uncontrolled and retrospective nature of the present series we cannot comment on time-dependent hemodynamic changes that could have contributed to the observed changes in hemodynamic parameters. Moreover, an effect of analgosedation on the hemodynamics cannot completely be denied. However, we feel that the marked hemodynamic changes cannot be explained by neither the natural time related course nor by the effects of analgosedation for several reasons. First, the pronounced decrease in systemic vascular resistance is not a hallmark in the hemodynamic course of *early* cardiogenic shock. Second, the potential influence of analgosedation is of minor importance, since it was initiated 24 ± 8 h before the beginning of the LS infusion and, on the large scale, the dose of analgosedation remained constant during the 24-h observation period.

In conclusion, the present series demonstrates that a LS infusion is feasible and may improve hemodynamics in severely compromized patients with cardiogenic shock. A significant hemodynamic effect of LS can be expected in such patients comparable to that observed in stable congestive heart failure patients. Due to its unique mode of action LS may be of value as add-on therapy in patients with cardiogenic shock. Its potential advantages when compared with other inotropes are unclear. To clarify the potential role of LS in this clinical setting randomized controlled trials on hemodynamic and mortality endpoints are needed. The design of these trials might include the no bolus strategy and follow-up times of 12–24 h for hemodynamic endpoints. Renal or hepatic impairment do not seem to result in obvious clinical problems if the use of LS is restricted to the time approved in congestive heart failure patients.

References

1. Hochman JS, Boland J, Sleeper LA et al. Current spectrum of cardiogenic shock and effect of early revascularization on mortality. Results of an International Registry. *Circulation* 1995; **9**: 873–81.

2. Pae WE, Miller CA, Matthews Y, Pierce WS. Ventricular assist devices for postcardiotomy cardiogenic shock. A combined registry experience. *J Thorac Cardiovasc Surg* 1992; **104**: 541–52.
3. Hasdai D, Topol EJM, Califf R, Berger PB, Holmes DR. Cardiogenic shock complicating acute coronary syndromes. *Lancet* 2000; **356**: 749–56.
4. Cotter G, Kaluski E, Blatt A et al. L-NMMA (a nitric oxide synthase inhibitor) is effective in the treatment of cardiogenic shock. *Circulation* 2000; **101**: 1358–61.
5. Haikala H, Levijoki J, Linden IB. Troponin C-mediated calcium sensitization by levosimendan accelerates the proportional development of isometric tension. *J Mol Cell Cardiol* 1995; **27**: 2155–65.
6. Packer M. The search for the ideal positive inotropic agent. *N Engl J Med* 1993; **329**: 201–2.
7. Slawsky MT, Colucci WS, Gottlieb SS et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. *Study Invest Circulation* 2000; **102**: 2222–7.
8. Nieminen MS, Akkila J, Hasenfuss G et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. *J Am Coll Cardiol* 2000; **36**: 1903–12.
9. Follath F, Cleland JGF, Just H et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomized double blind trial. *Lancet* 2002; **360**: 196–202.
10. Moiseyev VS, Poder P, Andrejevs N et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. *Eur Heart J* 2002; **23**: 1422–32.
11. Jamali IN, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Intracoronary levosimendan enhances contractile function of stunned myocardium. *Anesth Analg* 1997; **85**: 23–9.
12. Lilleberg J, Nieminen MS, Akkila J et al. Salmenperä. Effects of a new calcium sensitizer, levosimendan, on hemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. *Eur Heart J* 1998; **19**: 660–8.
13. Nijhawan N, Nicolosi A, Montgomery MW, Aggrawal A, Pagel PS, Warltier DC. Levosimendan enhances cardiac performance after cardiopulmonary bypass: a prospective, randomized placebo-controlled trial. *J Cardiovasc Pharmacol* 1999; **34**: 219–28.
14. McGough MF, Pagel PS, Lowe D, Hettrick DA, Warltier DC. Levosimendan potentiates the inotropic actions of dopamine in conscious dogs. *J Cardiovasc Pharmacol* 1996; **28**: 36–47.
15. Califf RM, Bengtson JR. Cardiogenic shock. *N Engl J Med* 1994; **16** (330): 1724–30.
16. Ryan TJ, Antman EM, Brooks NH et al. 1999 update. ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1999; **34**: 890–911.
17. Siostrzonek P, Koreny M, Delle-Karth G, Haumer M, Koller-Strametz J, Heinz G. Milrinone therapy in catecholamine-dependent critically ill patients with heart failure. *Acta Anaesthesiol Scand* 2000; **44**: 403–9.
18. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikaienen PJ. Pharmacodynamics and safety of a new calcium sensitizer, levosimendan and its metabolites during extended infusion in patients with severe heart failure. *J Clin Pharmacol* 2002; **42**: 43–51.

Address:
Dr Georg Delle Karth
Universitätsklinik für Innere Medizin
Kardiologie
Waehringer Guertel 18–20
A-1090 Vienna
Austria
e-mail: georg.delle-karth@univie.ac.at