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Safety and Effectiveness of Levosimendan in Patients with Predominant Right Heart Failure

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Abstract

Background and Purpose: Levosimendan is a new calcium sensitizer that enhances the contractile force of the myocardium and exhibits additional vasodilating properties. The present study describes the hemodynamic effects of levosimendan in patients with acute predominant right heart failure in need of inotropic therapy.

Patients and Methods: 18 patients (15 male, age 60 ± 17 years) with acute heart failure, predominant right ventricular dysfunction, left ventricular ejection fraction (LVEF) ≤ 30%, cardiac index (CI) ≤ 2.5 l/min/m², right atrial pressure (RAP) ≥ 10 mmHg, and pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg were investigated. Following a loading dose, levosimendan was administered intravenously for 24 h.

Results: After 24 h, CI and left ventricular stroke work index increased from 1.7 ± 0.4 to 2.3 ± 0.6 l/min/m² ($p < 0.001$) and 14 ± 6 to 17.3 ± 8 g-m/m²/beat ($p < 0.05$), respectively. PCWP and systemic vascular resistance decreased from 25 ± 7 to 21 ± 5 mmHg ($p < 0.01$) and 1,724 ± 680 to 1,096 ± 312 dyne * s * cm^{-5} ($p < 0.0001$), respectively. RAP was reduced from 15 ± 5 to 10 ± 3 mmHg ($p < 0.001$), whereas decreases in mean pulmonary artery pressure and pulmonary vascular resistance were not significant. Right ventricular stroke work index (RVSWI) increased from 4.8 ± 1.8 to 7.6 ± 3.4 g-m/m²/beat ($p < 0.01$).

Conclusion: Levosimendan therapy is feasible and improves hemodynamics in patients with acute predominant right heart failure. Augmentation in RVSWI indicates an increase in right ventricular contractility rather than reduction in afterload as a possible pathophysiological mechanism.

Sicherheit und Effektivität von Levosimendan bei Patienten mit akutem, überwiegendem Rechtsherzversagen

Schlüsselwörter:
Akute Herzinsuffizienz · Rechtsherzversagen · Levosimendan · Rechtsventrikulärer Schlagarbeitsindex

Zusammenfassung

Hintergrund und Ziel: Levosimendan ist ein Calciumsensitizer mit positiv inotroper und vasodilatierender Wirkung, dessen Anwendung sich bei der akuten Herzinsuffizienz als sehr effektiv erwiesen hat. In der vorliegenden Untersuchung wurden speziell die Wirkung und Sicherheit dieser neuen Substanz bei Patienten mit überwiegendem Rechtsherzversagen untersucht.

Patienten und Methodik: In einer Serie von 18 Patienten mit hochgradig eingeschränkter überwiegend rechtsventrikulärer Pumpfunktion, deutlich reduziertem Herzindex (CI), erhöhtem Wedge-Druck (PCWP) und klinischen Zeichen eines manifesten Rechtsherzversagens wurde Levosimendan als 24-h-Infusion mit und ohne vorausgehenden Bolus verabreicht.

Ergebnisse: Dabei bestätigten sich die bereits bekannten positiven Effekte auf die Hämodynamik (Zunahme des CI von 1,7 ± 0,4 auf 2,3 ± 0,6 l/min/m²; $p < 0{,}001$; Abnahme des PCWP von 25 ± 7 auf 21 ± 5 mmHg; $p < 0{,}01$; Abnahme des systemischen Gefäßwiderstands von 1 724 ± 680 auf 1 096 ± 312 dyn * s * cm^{-5}; $p < 0{,}0001$). Auffällig waren die Abnahme des rechtsatrialen Drucks von 15 ± 5 auf 10 ± 3 mmHg ($p < 0{,}001$) und die signifikante Steigerung des rechtsventrikulären Schlagarbeitsindex von 4,8 ± 1,8 auf 7,6 ± 3,4 g-m/m²/Schlag ($p < 0{,}01$) bei weitgehend unverändertem Lungengefäßwiderstand. Der Herzfrequenzanstieg während der Behandlung war nicht signifikant, und es traten keine Tachykardien und/oder relevanten Arrhythmien auf. Patienten mit vasopressorpflichtiger Hypotonie bereits zu Beginn oder während der Behandlung wiesen die höchste 30-Tage-Mortalität auf.

Schlussfolgerung: In dieser Fallserie erwies sich die Anwendung von Levosimendan bei Patienten mit überwiegender Rechtsherzdekompensation als sicher und effektiv. Die deutliche Zunahme der rechtsventrikulären Schlagarbeit spricht eher für die Kontraktilitätssteigerung des Ventrikels und weniger für die Nachlastsenkung als dem zugrundeliegenden Wirkmechanismus von Levosimendan am rechten Ventrikel.

Introduction

Levosimendan is a promising new calcium sensitizer that causes hemodynamic improvement in patients with acute heart failure. Although the effects of levosimendan on general hemodynamics and left ventricular failure have been shown in previous studies, little attention has been paid to its effects on right ventricular dysfunction [1]. Right heart failure was a widely neglected medical condition that has just recently gained interest. New data indicate a similar incidence of right and left ventricular failure, and mortality is unexpectedly high in patients with cardiogenic shock due to right ventricular infarction [2–4].

Therapeutic options are limited in right heart failure aside from correcting reversible causes such as ischemia and arrhythmias. Volume loading can increase right ventricular preload and cardiac output but is limited beyond critical pulmonary artery pressure (PAP) [5]. Additionally, positive inotropic agents have been associated with increased myocardial oxygen consumption and arrhythmias [6].

Levosimendan has been shown to generate positive inotropic effects in the left ventricle, as well as mediate systemic vasodilation by a hybrid mode of action [7]. The substance increases calcium sensitivity of myofilaments by directly targeting troponin C and activating adenosine triphosphate-sensitive potassium (K^+) channels in the heart and systemic arteries [8, 9]. In clinical trials' treatment of acute heart failure patients, levosimendan was associated with beneficial hemodynamic effects as well as a favorable impact on mortality [10–12]. However, only few data is available on the effects of levosimendan in patients with biventricular or predominant right ventricular failure.

We hypothesized that intravenous therapy with levosimendan is feasible in patients with acute predominant right ventricular failure in need of inotropic therapy, and that levosimendan improves right ventricular hemodynamic parameters.

Patients and Methods

Patients

18 patients who met the following criteria were selected for retrospective analysis from a consecutive series of 37 patients treated with levosimendan in a 14-bed intensive care unit at a university hospital: acute heart failure, severe right ventricular dysfunction, left ventricular ejection fraction (LVEF) ≤ 30%, cardiac index (CI) ≤ 2.5 l/min/m^2, right atrial pressure (RAP) ≥ 10 mmHg, and pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg. Predominant right heart failure was defined by the additional presence of at least three out of four of the following physical signs: jugular venous distension, liver enlargement, ascites, and edema.

Echocardiography

Biplane Simpson's rule was applied for quantitative assessment of left ventricular dysfunction. Right ventricular function was assessed semiquantitatively.

Hemodynamic Measurements

Arterial blood pressure measurements were performed using an indwelling arterial cannula inserted into the radial artery. PAP, RAP and PCWP were obtained at end-expiration with a 7.5-F balloon-tipped pulmonary artery Swan-Ganz thermodilution catheter (Model 831HF75, Edwards Lifesciences, Irvine, CA, USA) at baseline, 30 min, 1 h, 6 h, 12 h, and 24 h after the start of levosimendan. Cardiac output measurements were performed in triplicate in patients in sinus rhythm and five times in patients in atrial fibrillation, respectively, using a closed injectate delivery cardiac output set (Model 93600, Edwards Lifesciences) and 10 ml of cooled saline in combination with the cardiac output computer integrated into the bedside monitor (HP-CMS M1046, Hewlett-Packard, Andover, MA, USA). Standard formulas were applied for calculation of left (LVSWI) and right ventricular stroke work indices (RVSWI) and resistances. Heart rate (HR), rhythm, blood pressure (BP), and arterial oxygen (O_2) saturation were continuously monitored.

Levosimendan Treatment

Treatment with levosimendan (marketed by Abbott Ges.m.b.H, Vienna, Austria, as Simdax®) was started with a loading dose of 6–12 µg/kg/min over 10 min, followed by a continuous infusion of 0.075–0.2 µg/kg/min for 24 h. If necessary, vasopressor therapy was added to maintain a mean arterial pressure (MAP) of > 65 mmHg. Treatment with diuretics was withheld for the first 4 h of therapy and then adjusted at the discretion of the attending physician. Conversely, treatment with fluids was added to maintain a PCWP of > 12 mmHg.

Statistical Analysis

Changes in hemodynamic parameters over the study period were analyzed by using analysis of variance for repeat measurements (in case of normally distributed variables) or the nonparametric Friedman test in all other cases. Normality assumption was checked using the Shapiro-Wilks test. Multiple comparisons versus baseline were corrected applying the Bonferroni procedure. Data are presented as mean ± SD (standard deviation). A p-value of < 0.05 was considered significant.

Table 1. Baseline characteristics of patients. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction.

Tabelle 1. Patientencharakteristika vor Beginn der Therapie. ACEI: Angiotensinkonversionsenzymhemmer; ARB: Angiotensin-II-Rezeptor-Blocker; BNP: natriuretisches Peptid vom B-Typ; LVEF: linksventrikuläre Ejektionsfraktion.

Age (years)	60 (±17)
Sex: male/female (n)	15/3
LVEF (%)	20 (±7)
BNP (pg/ml)	796 (±498)
Acute on chronic heart failure [n (%)]	12 (67)
De novo heart failure [n (%)]	6 (33)
• Myocardial infarction (n)	4
• Myocarditis (n)	1
• Graft failure (n)	1
Neurohormonal therapy at baseline	
• ACEI/ARB [n (%)]	14 (78)
• β-blocker [n (%)]	6 (33)

Results

Patient characteristics and hemodynamic parameters at baseline and after 24 h of levosimendan therapy are shown in Tables 1 and 2, respectively. Levosimendan treatment resulted in a significant increase in CI, mixed venous oxygen saturation (SvO_2), and LVSWI (26% ± 39%), and a significant decrease in PCWP and systemic vascular resistance (SVR; Table 2 and Figure 1a). MAP was significantly reduced, whereas a small increase in HR was not significant (Table 2).

Table 2 and Figure 1b depict changes in right ventricular hemodynamics. RAP was significantly reduced. By contrast, small decreases in mean pulmonary artery pressure (PAPm) and in pulmonary vascular resistance (PVR) were not statistically significant. Importantly, there was a highly significant increase in RVSWI (74% ± 95%) whereas the increase in pressure gradient from RAP to PAPm did not reach statistical significance. Consistently, the relationship between RA and CI was shifted leftward and upward (Figure 2).

No loading dose of levosimendan was given in six patients because of severe hypotension (MAP < 65 mmHg) at baseline. In these patients, levosimendan was started at a maintenance dose of 0.1 µg/kg/min, which was supported by vasopressor therapy with either dopamine or norepinephrine in four patients. Hypotension due to systemic vasodilation rather than to volume depletion ensued in another three patients during the first hours of therapy. These patients were also supported with a vasopressor. Weaning from vasopressor therapy during the course of levosimendan was possible in all but three patients.

Levosimendan was well tolerated by all patients, and episodes of tachycardia and arrhythmias were not noted. Levosimendan was not discontinued prematurely in any of the patients. Following 30 days after levosimendan treatment, eight patients (44%) remained event-free, one patient (6%) had to be rehospitalized for recurrent heart failure, and three patients (17%) underwent implantation of a ventricular assist device and heart transplantation, respectively. Six patients (33%) died, due to refractory cardiogenic shock (three patients), sepsis (two patients), and sudden cardiac death (one patient). Notably, all of the latter patients needed vasopressor support during the course of levosimendan, with three of the patients requiring vasopressors from the very beginning.

Table 2. Hemodynamic parameters at baseline and after 24 h of levosimendan therapy. CI: cardiac index; HR: heart rate; LVSWI: left ventricular stroke work index; MAP: mean arterial pressure; NS: not significant; PAPm: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RVSWI: right ventricular stroke work index; SvO_2: mixed venous oxygen saturation; SVR: systemic vascular resistance.

Tabelle 2. Hämodynamische Parameter vor und nach 24-stündiger Therapie mit Levosimendan. CI: Herzindex; HR: Herzfrequenz; LVSWI: linksventrikulärer Schlagarbeitsindex; MAP: mittlerer arterieller Druck; NS: nicht signifikant; PAPm: mittlerer pulmonalarterieller Druck; PCWP: Wedge-Druck; PVR: Lungengefäßwiderstand; RAP: rechtsatrialer Druck; RVSWI: rechtsventrikulärer Schlagarbeitsindex; SvO_2: gemischt-venöse Sauerstoffsättigung; SVR: systemischer Gefäßwiderstand.

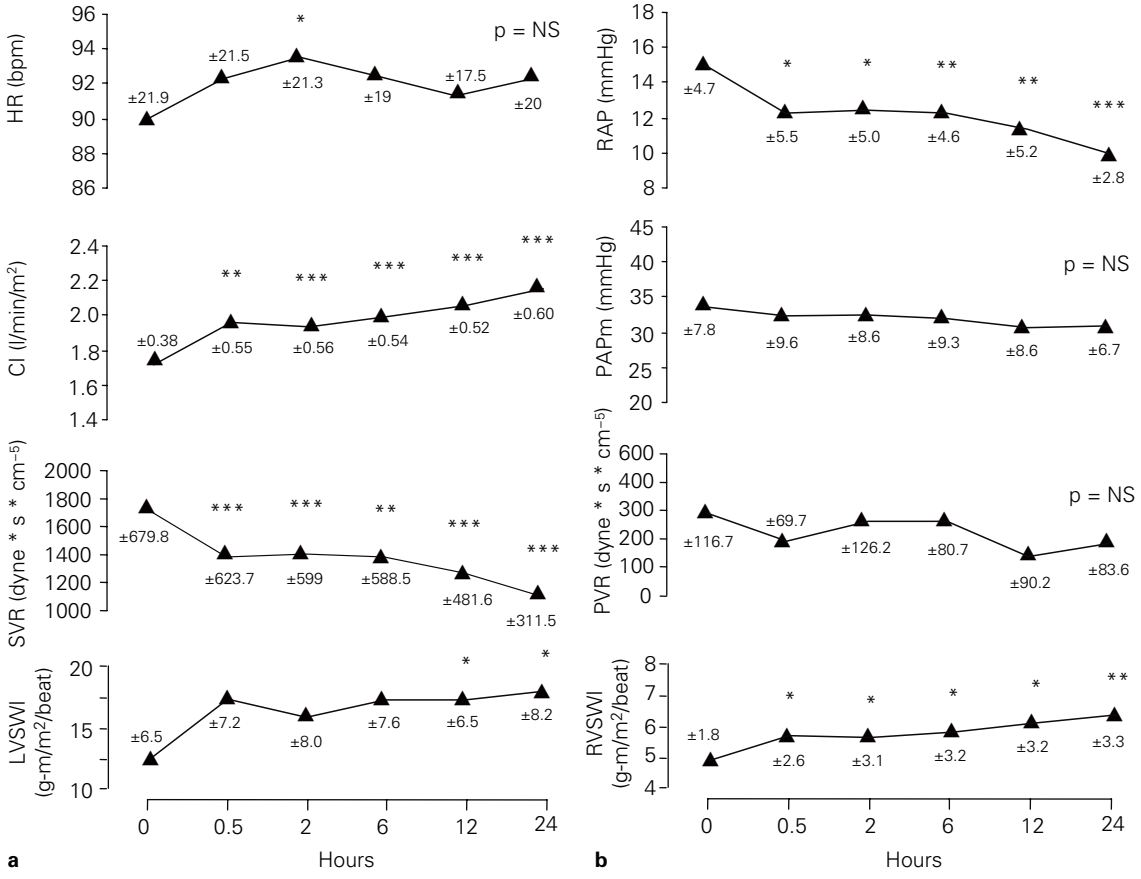
Parameter	Baseline	24 h	p-value
HR (bpm)	90 ± 22	92 ± 20	NS
CI (l/min/m²)	1.7 ± 0.4	2.3 ± 0.6	< 0.001
SvO_2 (%)	54 ± 8	64 ± 8	< 0.0001
MAP (mmHg)	78 ± 13	70 ± 15	< 0.01
PCWP (mmHg)	25 ± 7	21 ± 5	< 0.01
SVR (dyne * s * cm^{-5})	1,724 ± 680	1,096 ± 312	< 0.0001
LVSWI (g-m/m²/beat)	14 ± 6	17.3 ± 8	< 0.05
PAPm (mmHg)	34 ± 8	32 ± 7	NS
RAP (mmHg)	15 ± 5	10 ± 3	< 0.001
PAPm – RAP (mmHg)	19 ± 6	22 ± 6	0.079
PVR (dyne * s * cm^{-5})	264 ± 116	209 ± 107	NS
RVSWI (g-m/m²/beat)	4.8 ± 1.8	7.6 ± 3.4	< 0.01

Discussion

The present series of patients with acute predominant right heart failure shows that levosimendan therapy is feasible and effective in this critically ill population. The hemodynamic improvement was comparable to what has been shown in previous clinical trials in acute and chronic heart failure patients. Thus, our findings extend previous data on levosimendan to a population with severely compromised right ventricular function.

Improvement in left ventricular hemodynamics in our patients was in accordance with findings in previous studies [10, 11, 13, 14]. A 24-h course of levosimendan resulted in a significant increase in CI along with a significant decrease in SVR and left ventricular preload.

Right ventricular failure is characterized by reduced right ventricular ejection into the pulmonary circulation due to severely impaired pressure genera-



Figures 1a and 1b. Changes in heart rate (HR), cardiac index (CI), systemic vascular resistance (SVR), left ventricular stroke work index (LVSWI; a), and in right atrial pressure (RAP), mean pulmonary artery pressure (PAPm), pulmonary vascular resistance (PVR), and right ventricular stroke work index (RVSWI; b) before, during and after the course of levosimendan therapy. *p < 0.05; **p < 0.001; ***p < 0.0001.

Abbildungen 1a und 1b. Änderungen von Herzfrequenz (HR), Herzindex (CI), systemischem Gefäßwiderstand (SVR) und linksventrikulärem Schlagarbeitsindex (LVSWI; a) sowie von rechtsatrialem Druck (RAP), mittlerem pulmonalarteriellen Druck (PAPm), Lungengefäßwiderstand (PVR) und rechtsventrikulärem Schlagarbeitsindex (RVSWI; b) vor, während und nach Behandlung mit Levosimendan. *p < 0,05; **p < 0,001; *** p < 0,0001.

tion in the right ventricle, with diminished pressure gradient from the right atrium to the pulmonary artery [1]. The inability to maintain low RAP leads to progressive venous volume overload.

In our series of patients with predominant right heart failure, intravenous application of levosimendan resulted in a decrease in right ventricular preload and a significant increase in RVSWI. This was mirrored by a clear leftward and upward shift of the relationship between right ventricular preload and cardiac output. Pulmonary vascular function as assessed by PVR remained largely unaffected. In contrast to our findings, previous data by Slawsky et al. showed a significant decrease of PVR with levosimendan [13]. A possible explanation for this difference might be the higher dose of levosimendan used in the study by Slawsky et al. Consistently, Nieminen et al. have shown a linear dose relationship of changes in PVR for levosimendan [14].

Hence, our findings indicate an augmentation in right ventricular contractility by levosimendan.

The concept of levosimendan's predominant effect on right ventricular contractility is supported by experimental data published by Leather et al. [15]. In an open chest pig model, levosimendan enhanced right ventricular contractility and performance without significantly influencing pulmonary vascular tone. Importantly, in this study improvement of right ventricular performance was not associated with a relevant increase in O_2 consumption. The latter is also consistent with data from clinical studies examining the human left ventricle [16].

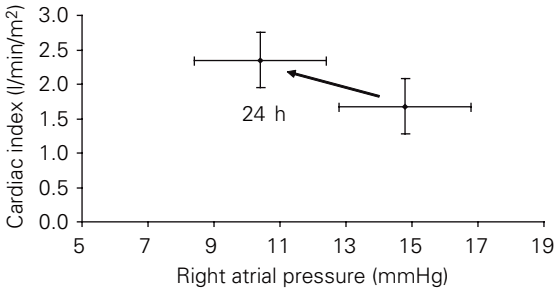


Figure 2. Relationship between right ventricular preload (RAP) and cardiac index before and after levosimendan therapy. Levosimendan therapy resulted in a clear leftward and upward shift of the Frank-Starling curve.

Abbildung 2. Beziehung zwischen rechtsventrikulärer Vorlast (RAP) und Herzindex vor und nach Behandlung mit Levosimendan. Levosimendan verursacht eine deutliche Linksverschiebung der Frank-Starling-Beziehung am rechten Ventrikel.

In the present series, the effects of levosimendan on right and left ventricular hemodynamic parameters appear to be somewhat different. The vasodilator response, which is compatible with levosimendan's known potassium channel-activating effects in vascular smooth muscle cells, was stronger in the systemic vasculature compared to the pulmonary circulation. Conversely, the positive inotropic effect, as indirectly assessed by the percentage increase in stroke work index, appears higher in right compared to left ventricle. This may indicate an augmentation of right ventricular contractility rather than afterload reduction as levosimendan's principal mode of action in right ventricular dysfunction. However, further investigation is needed to determine whether these differences in the effects of levosimendan on right and left ventricular hemodynamic parameters are essential.

In this study of patients with predominant right heart failure, levosimendan was effective and well tolerated. In particular, there was only a small increase in mean HR, and none of the patients experienced tachycardia or other arrhythmic events. Hence, these findings may extend the current therapeutic indications of levosimendan to patients with physical signs of right heart failure, elevated right ventricular preload and afterload, and low cardiac output. It should be noted, though, that hypotension, not related to volume depletion, either at baseline or during the course of levosimendan, poses a serious threat in this group of patients. Although four out of seven patients in our case series could be weaned from vasopressor support within 24 h, six patients died within the next 30 days. Patients in need of additional vasopressor therapy may thus constitute an especially high-risk population. It cannot be excluded that levosimendan's vasodilating properties may aggravate the deleterious impact of hypotension and the toxic effects of vasopressor therapy in these high-risk patients. Hence, caution is indicated in dosing of levosimendan and a loading dose should be avoided.

The present findings are clearly limited by the uncontrolled nature of the study and by the small number of patients. Hence, the results have to be interpreted with caution. Nevertheless, a growing body of evidence indicates that levosimendan enhances contractile function and produces beneficial hemodynamic effects in acute heart failure patients. Therefore, it appears likely that levosimendan may also exert favorable effects in acute right heart failure. This hypothesis, however, remains to be tested in a prospective controlled trial particularly in patients with isolated right heart failure.

A further limitation arises from the fact that right ventricular function has been evaluated semiquantitatively by echocardiography at baseline and no follow-up data is available. Also, direct assessment of right ventricular contractility would have increased the significance of the study.

Conclusion

Our findings indicate that levosimendan therapy is feasible and improves hemodynamic parameters in patients with acute predominant right ventricular failure. Augmentation in right ventricular stroke work and leftward shift of the relationship between right ventricular preload and cardiac output indicate an increase in right ventricular contractility rather than afterload reduction as the underlying mechanism. Prospective studies with larger numbers of patients are needed to support this concept.

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