Valvular Heart Disease

Effects of Levosimendan on Left Ventricular Relaxation and Early Filling at Maintained Preload and Afterload Conditions After Aortic Valve Replacement for Aortic Stenosis

Kirsten Jörgensen, MD; Odd Bech-Hanssen, MD, PhD;
Erik Houltz, MD, PhD; Sven-Erik Ricksten, MD, PhD

Background—We determined the effects of levosimendan, a calcium sensitizer, on left ventricular (LV) diastolic function in patients with LV hypertrophy.

Methods and Results—In this prospective, randomized, blinded study, 23 patients received either levosimendan (0.1 and 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$; n=12) or placebo (n=11) after aortic valve replacement for aortic stenosis. The effects on LV performance, dimensions, filling patterns, and isovolumic relaxation time, as well as systemic hemodynamics, were assessed by pulmonary artery thermodilution catheterization and transesophageal 2-dimensional Doppler echocardiography. To circumvent the confounding effects of the levosimendan-induced hemodynamic changes on Doppler echocardiographic indexes of LV early relaxation, heart rate and mean arterial and central venous pressures were kept constant during levosimendan/placebo infusion by atrial pacing, vasopressor, and colloid infusions. In the levosimendan group, dose-dependent increases in cardiac output (28%; $P<0.001$) and stroke volume (26%; $P<0.001$) and a decrease in systemic vascular resistance (-22%; $P<0.001$) were observed. There was a trend for an increase in LV ejection fraction (12%; $P=0.058$) with levosimendan. There were no significant differences in systolic, diastolic arterial, or LV filling pressures or LV end-diastolic area between the 2 groups. Isovolumic relaxation time decreased (-23%; $P<0.001$), as did the deceleration slope of early diastolic filling (-45%; $P<0.01$), whereas peak early diastolic filling velocity (16%, $P<0.01$) and peak late diastolic filling velocity (15%; $P<0.001$) increased after levosimendan compared with placebo.

Conclusion—Levosimendan, in addition to its inotropic effects, exerts a direct positive lusitropic effect in patients with LV hypertrophy as it shortens isovolumic relaxation time and improves LV filling. (***Circulation***. 2008;117:1075-1081.)

Key Words: diastole ■ echocardiography ■ hypertrophy ■ simendan ■ stenosis

Levosimendan offers new therapeutic possibilities in patients with severe heart failure because of its combined inotropic and vasodilatory effects.[1] This drug enhances myocardial contractility through myofilament calcium sensitization by binding to troponin-C in a calcium concentration–dependent manner and induces peripheral and coronary vasodilation by opening ATP-sensitive potassium channels.[2,3]

Clinical Perspective p 1081

Left ventricular (LV) systolic dysfunction often is accompanied by impaired LV relaxation,[4] and increased sensitivity to calcium during diastole would further impede relaxation of the heart and worsen diastolic dysfunction. The effects of calcium sensitizers on myocardial relaxation and diastolic function in humans, however, are incompletely understood. In vitro studies have shown that calcium sensitizers (EMD 57033, ORG 30029) may impair myocardial relaxation and elevate diastolic tension in failing human myocardium,[5] whereas levosimendan, on the other hand, has been shown to improve both systolic and diastolic function of cardiac muscle preparations from end-stage failing human hearts.[6]

Furthermore, it has recently been suggested that levosimendan improves Doppler echocardiographic variables of LV diastolic function both in patients with severe heart failure[7,8] and in patients with acute myocardial infarction.[9] These findings, however, should be interpreted with caution because these Doppler echocardiographic indexes are preload, afterload, and heart rate dependent.[10–12] Because of the well-known effects of levosimendan on preload, afterload, and heart rate,[1] it is difficult to evaluate the potential direct effect of levosimendan on LV early relaxation, ie, the lusitropic effect, because the positive chronotropic and vasodilatory effects of levosimendan affect the Doppler echocardiographic indexes used to evaluate early LV relaxation to a great extent.

Circulation is available at http://circ.ahajournals.org

In the present randomized, blinded, placebo-controlled study, we evaluated the effects of levosimendan versus placebo on LV early relaxation in patients with LV hypertrophy and maintained systolic function in patients undergoing aortic valve surgery for severe aortic stenosis. In the operating room, after valve replacement, LV performance, dimensions, and filling pattern, as well as systemic hemodynamics, were assessed by transesophageal 2-dimensional Doppler echocardiography and pulmonary artery catheterization. To circumvent the confounding effects of the levosimendan-induced hemodynamic changes on Doppler echocardiographic indexes of LV early relaxation, heart rate, preload, and afterload were kept constant by atrial pacing, by blood volume expansion with colloids, and by phenylephrine-induced vasoconstriction, respectively. We hypothesized that levosimendan improves LV early relaxation in patients with LV hypertrophy and diastolic dysfunction.

Methods

Patients

The local ethics committee of the medical faculty of Göteborg University approved the study protocol. After informed consent was obtained, a randomized, prospective, blinded, placebo-controlled study was performed involving 23 consecutive symptomatic patients with aortic stenosis scheduled for aortic valve replacement or aortic valve replacement plus coronary artery bypass grafting. Inclusion criteria were (1) aortic valve area <1 cm^2 estimated by the continuity equation, a mean aortic valve pressure gradient >50 mm Hg; (2) preoperative ejection fraction of $>50\%$; (3) LV septal wall thickness >11 mm; (4) less than moderate aortic insufficiency; (5) coronary artery disease as a secondary finding on routine cardiac catheterization; (6) sinus rhythm before and after cardiopulmonary bypass (CPB); and (7) uncomplicated weaning from CPB with no need for inotropic support. Patients with previously documented coexisting valve disease such as moderate mitral or mild tricuspid insufficiency or aortic subvalvular LV outflow tract obstruction were excluded from the study. Inclusion and exclusion criteria were confirmed by initial intraoperative transesophageal echocardiographic evaluation.

Anesthesia

The patients were premedicated with flunitrazepam (0.5 to 1 mg) orally and morphine (5 to 10 mg) and scopolamine (0.2 to 0.4 mg) subcutaneously. β-Adrenergic blockers were continued during the perioperative period, including the morning of surgery. Anesthesia was induced with thiopental (1 to 3 mg/kg) and fentanyl (5 to 10 μg /kg). Tracheal intubation was facilitated with pancuronium (0.1 mg/kg). Before and after CPB, anesthesia was maintained with sevoflurane in oxygen/air with an FIO_2 necessary to keep P$_a$O$_2$ >20 kPa. During CPB, a continuous infusion of propofol was administered. Ventilation was volume controlled to maintain P$_a$CO$_2$ between 4.0 and 5.0 kPa. Intraoperative hypotension was treated with fluids, phenylephrine infusion, or both, and hypertension was treated with sodium nitroprusside infusion. Target mean arterial blood pressure during CPB was 50 to 90 mm Hg. Hemoglobin was kept at >10g/dL by infusion of erythrocyte-enriched blood products when necessary.

Surgery

CPB was performed with a COBE Duo membrane oxygenator (COBE, Arvada, Colo) after administration of heparin (300 U/kg). The activated clotting time was maintained at >400 seconds. The circuit was primed with 1500 mL Ringer's solution and 200 mL mannitol (15%), and a nonpulsatile flow of 2.4 L $\cdot$ min^{-1} $\cdot$ m^{-2} was used. Hypothermia (32°C to 34°C) and cold hyperkalemic blood cardioplegia were used during CPB. The cross-clamp was removed, and coronary perfusion was reestablished. After rewarming (36.5°C to 37°C), the CPB was discontinued. No inotropic drugs were administered prophylactically during weaning from the CPB. The heparin effect was reversed with protamine sulfate until normal activated clotting time values were achieved.

Hemodynamic Measurements

Arterial blood pressure was monitored with a femoral artery catheter. After induction of anesthesia, a pulmonary artery thermodilution catheter (131HF7, TD Baxter Healthcare Corp, Irvine, Calif) was inserted through the right internal jugular vein into the pulmonary artery. Continuous recordings of heart rate and systolic, diastolic, and mean arterial pressures, together with systolic, diastolic, mean pulmonary artery, and central venous pressures, were performed. Thermodilution cardiac output in triplicate and pulmonary capillary wedge pressure measurements were performed at each measuring point. Stroke volume, stroke work, systemic vascular resistance, and pulmonary vascular resistance were calculated and indexed to the patient's body surface area.

Two-Dimensional Echocardiography

A multiplane transesophageal echocardiographic transducer (ACUSON, ACUSON Corp, Mountain View, Calif) was used, together with a Sequoia echocardiography system (Sequoia c256, ACUSON Corp). Using the midpapillary short-axis image of the left ventricle, we outlined the LV endocardial border in end systole and end diastole and calculated LV end-systolic and end-diastolic areas, together with area ejection fraction (AEF). End-systolic and end-diastolic areas were indexed to the patient's body surface area (ESAI and EDAI, respectively). Images were stored on magneto-optical disks and later transferred to a computer system (EchoPac PC Dimension version 4.0.x., GE Medical Systems, Milwaukee, Wis) for offline analysis.

Mitral Doppler Measurements

After completion of the LV short-axis measurements, the transducer was withdrawn until a long-axis image was obtained in the midesophageal 4-chamber view. A pulsed Doppler line was positioned with the measuring caliper at the tips of the mitral leaflets and adjusted to be as parallel as possible to the mitral flow. The Doppler flow profiles were recorded on magneto-optical disk. These flow profiles were later transferred to a computer and evaluated with a digitizing tablet by means of a PC-based analysis system (Echo Pac PC Dimension version 4.0.x.). Three consecutive beats were digitized, and their mean values were used for analysis. The following variables were derived from the mitral Doppler tracings: peak early diastolic and peak late diastolic filling velocities (E-max and A-max, respectively), deceleration rate (E-dec slope), and deceleration time (E-dec time) of early diastolic filling. The ratio of E-max to A-max (E/A) was calculated.

Isovolumic relaxation time (IVRT), which is the interval between closure of the aortic valve and opening of the mitral valve, was measured by first positioning the Doppler sample volume at the tips of the mitral leaflets (midesophageal 4-chamber view) to measure the time distance from the R wave of the ECG to the beginning of the E wave, t^E. Thereafter, the Doppler sample volume was positioned at the aortic valve (midesophageal aortic valve short-axis view) to measure the time distance from the R wave to the aortic valve closure, t^A. IVRT was calculated by subtracting t^A from t^E (Figure 1). Isovolumic contraction time (IVCT) was measured as the time distance from the R wave to the aortic valve opening.

Experimental Protocol

The experimental procedure was performed in the operating room after completion of surgery. The patient was positioned in the supine position and sedated with sevoflurane at an end-tidal concentration of 1%. All patients had sinus rhythm and were subjected to atrial pacing by external pacemaker wires to establish a constant heart rate, 5% to 10% over baseline, during the entire experimental procedure. Two baseline measurements of hemodynamic and echocardiographic data were obtained and immediately followed by infusion of placebo or levosimendan (0.05 mg/mL) at 2 infusion rates: 0.1 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} (dose 1) and 0.2 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} (dose 2) after initial loading doses of 12 μg/kg. The loading
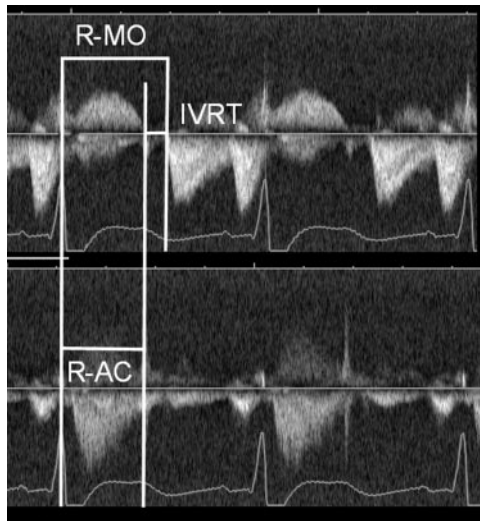
Figure 1. Continuous Doppler recording for calculation of IVRT. The time distance between the R wave of the ECG to the mitral valve opening (R-MO) and the time distance between the R wave and aortic closure (R-AC) were estimated. IVRT was defined as the difference between R-MO and R-AC.

doses of levosimendan were given over 10 minutes, followed by a continuous intravenous infusion for 20 minutes.

The placebo group received equivalent volumes of isotonic saline as initial loading doses followed by a continuous infusion of isotonic saline at rates equal to that of the study group. The investigators were blinded to the treatment (levosimendan or placebo) the patient was to receive. Mean arterial pressure was kept constant by infusion of a vasopressor (phenylephrine); central venous pressure was kept constant by infusion of hetastarch (Voluven, Fresenius Kabi, Bad Homburg, Germany). Measurements were performed at the end of each 30-minute treatment period during brief periods of apnea. One investigator obtained echocardiographic data while another performed hemodynamic measurements.

Statistical Analysis

Demographic, presurgical, and surgical variables and baseline data were compared using Student's unpaired t test or Fisher's exact test when appropriate. The reproducibility of the echocardiographic measurements (baseline 1 and baseline 2) was assessed from the 2 baseline recordings according to Bland and Altman.[13] The differential effects of the study drugs (levosimendan or placebo) were evaluated by 2-way ANOVA for repeated measurements on baseline, dose 1, and dose 2 data. A value of $P<0.01$ was considered statistically significant. Data are presented as mean±SEM.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Twenty-six patients scheduled for elective aortic valve replacement for aortic stenosis were enrolled and randomized to 1 of the 2 study groups. Three patients were excluded because of bleeding in the immediate postoperative period, 1 in the levosimendan group and 2 in the placebo group. Patient characteristics, preoperative Doppler echocardiography findings, patient presentation, preoperative medications and surgical data, CPB time, and aortic cross-clamp time are presented in Table 1. There were no differences between groups regarding the variables presented in Table 1. After separation from CPB, transesophageal echocardiography revealed normal prosthetic valve function and no evidence of abnormal

Table 1. Demographic and Surgical Variables

Variables	Levosimendan (n=12)	Placebo (n=11)
Patient characteristics		
Gender, F/M	4/8	6/5
Age, y	73±6	72±8
Height, cm	171±11	170±10
Weight, kg	74±16	78±17
BSA, m²	1.85±0.23	1.88±0.25
Doppler echo		
Aortic valve area, cm²	0.73±0.22	0.74±0.10
Aortic valve gradient, mm Hg	81±34	88±17
Ejection fraction, %	60±7	62±6
Presentation, n		
Hypertension	5	6
Congestive heart failure	12	10
Fatigue	3	2
Angina	4	4
Myocardial infarction	2	3
Syncope	4	3
Preoperative medications, n		
ACE inhibitor	3	1
β-Adrenergic blocker	8	6
Calcium antagonists	3	2
Digoxin	1	0
Diuretic	6	4
Insulin	1	0
Inhaled bronchodilator	3	1
Nitroglycerin	3	3
Surgical procedure		
Valve type (biological/mechanical)	9/3	8/3
Coronary artery bypass grafting	6	6
LAD/LCx/RCA	5/4/6	4/3/2
Valve size (21/23/25 mm), n	5/5/2	3/3/5
CPB time, min	119±38	106±29
Aortic cross-clamp time, min	96±33	84±25

BSA indicates body surface area; Doppler echo, preoperative Doppler echocardiography; ACE, angiotensin-converting enzyme; and LAD/LCx/RCA, left anterior descending, left circumflex, and right coronary artery. Values are mean±SD when appropriate.

flow velocities or LV outflow obstruction for all patients, with or without the administration of levosimendan.

The infusion rates of phenylephrine at baseline and the 2 infusion rates (dose 1 and dose 2) were 0.052±0.021, 0.26±0.081, and 0.26±0.076 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, for the levosimendan group. Corresponding infusion rates for the placebo group were 0.017±0.012, 0.101±0.082, and 0.112±0.091 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Pulmonary and Systemic Hemodynamics

Baseline hemodynamic data were similar for both groups (Table 2). In the levosimendan group, a dose-dependent significant increase in mean pulmonary artery pressure,

Table 2.   Systemic Hemodynamic Variables

Variables	Levosimendan			Placebo			P, ANOVA
	Baseline	Dose 1	Dose 2	Baseline	Dose 1	Dose 2	
SAP, mm Hg	107±3	110±3	111±3	107±5	112±7	112±7	0.945
DAP, mm Hg	52.8±2	53.1±2	52.7±2	52.0±2	54.6±3	54.6±3	0.216
MAP, mm Hg	72±2	73±2	72±2	71±3	74±4	75±5	NA
MPAP, mm Hg	21.5±1.0	24.0±1.1	25.9±1.5	20.5±0.9	21.1±1.1	20.8±1.0	0.002
PCWP, mm Hg	13.8±0.9	15.2±1.0	15.7±1.3	12.2±0.6	12.7±1.1	12.8±0.8	0.386
CVP, mm Hg	11.3±1.1	11.6±1.1	11.6±1.1	10.9±1.1	10.9±1.2	11.4±1.2	0.622
CI, L · min^{-1} · m^{-2}	2.32±0.13	2.69±0.17	2.96±0.18	2.27±0.16	2.20±0.18	2.21±0.18	<0.001
HR, bpm	75±2.0	75±2.0	75±1.9	70±1.2	70±1.2	70±1.2	NA
SVI, mL/m^2	31.3±1.8	36.0±2.3	39.4±2.6	32.3±2.2	31.4±2.5	31.4±2.6	<0.001
SWI, g · m · m^{-2}	24.4±1.5	28.2±1.6	29.8±2.2	26.1±2.7	26.7±3.4	27.6±3.7	0.035
SVRI, dynes · s · cm^{-5} · m^{-2}	2169±163	1935±184	1698±149	2190±155	2387±183	2352±137	<0.001
PVRI, dynes · s · cm^{-5} · m^{-2}	272±31	253±26	272±23	316±30	339±55	324±51	0.507

SAP indicates systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; HR, heart rate; SVI, stroke volume index; SWI, stroke work index; SVRI, systemic vascular resistance index; and PVRI, pulmonary vascular resistance index. Values are mean±SEM.

cardiac index, and stroke volume index and a dose-dependent significant decrease in systemic vascular resistance index were observed compared with placebo, whereas there were no significant differences in systolic arterial, diastolic arterial, pulmonary capillary wedge, central venous pressure, or pulmonary vascular resistance index between the 2 groups.

Two-Dimensional Echocardiographic Variable of the LV

Baseline EDAI, ESAI, and AEF were similar for both groups (Table 3). There was a trend for an increase in AEF in the levosimendan group compared with placebo ($P=0.058$), whereas there were no differences in EDAI or ESAI between the 2 groups.

Mitral Doppler Echocardiographic Variables, IVRT, and IVCT

At baseline, E-dec slope, E-dec time, E-max, A-max, E/A ratio, IVRT, and IVCT were similar for both groups (Table 4). In the levosimendan group, dose-dependent increases in E-max, A-max, and E-dec slope were noted, whereas there was a trend for a decrease in E-dec time ($P=0.06$) compared with placebo. There was no difference in E/A between groups. IVRT decreased dose dependently with levosimendan compared with placebo (Figure 2). There was a trend ($P=0.015$) for a decrease in IVCT with levosimendan.

There was good reproducibility for repeated estimation of EDAI, ESAI, AEF, E-dec slope, E-dec time, E-max, A-max, E/A, and IVRT. The mean difference between 2 measurements (bias), the SD of the differences, the error (double SD divided by the mean of the repeated measurements), and limits of agreement are shown in Table 5.

Discussion

In the present study, the effects of incremental infusion rates of levosimendan on LV relaxation and systolic performance were studied immediately after aortic valve replacement for aortic stenosis during controlled and maintained preload, afterload, and heart rate conditions. The main findings were that the beneficial effect of levosimendan on systolic performance was accompanied by an improvement in LV relaxation; that is, levosimendan has a positive lusitropic effect in patients with LV hypertrophy.

The effects of levosimendan on Doppler echocardiographic indexes of LV relaxation have previously been studied in patients with severe heart failure.[7,8] Thus, it was shown that levosimendan increased the LV IVRT and the E-dec time and decreased the E/A ratio. This reversal of the restrictive LV filling pattern into a "pseudonormal" filling pattern was interpreted as an improvement in LV diastolic function by levosimendan. However, the levosimendan-induced 30% decrease in left atrial pressure might explain the prolongation of the IVRT, as well as

Table 3.   LV Dimensions

Variables	Levosimendan			Placebo			P, ANOVA
	Baseline	Dose 1	Dose 2	Baseline	Dose 1	Dose 2	
EDAI, cm^2/m^2	10.4±0.3	11.4±0.3	10.6±0.4	9.7±0.5	10.6±0.6	10.2±0.6	0.528
ESAI, cm^2/m^2	6.0±0.4	6.1±0.3	5.6±0.4	5.4±0.5	6.0±0.5	5.6±0.4	0.213
AEF	0.43±0.03	0.46±0.02	0.48±0.03	0.45±0.03	0.44±0.03	0.45±0.02	0.057

Values are mean±SEM.

Table 4. Mitral Doppler Variables

Variables	Levosimendan			Placebo			P, ANOVA
	Baseline	Dose 1	Dose 2	Baseline	Dose 1	Dose 2	
E-dec slope, cm/s^{-2}	-347 ± 21	-427 ± 35	-504 ± 53	-302 ± 19	-317 ± 23	-318 ± 23	0.003
E-dec time, ms	238 ± 12	213 ± 13	201 ± 15	240 ± 14	235 ± 13	227 ± 14	0.060
E-max, cm/s	81.0 ± 4.7	88.0 ± 5.7	93.8 ± 5.0	72.0 ± 5.7	73.6 ± 5.9	71.9 ± 5.8	0.010
A-max, cm/s	65.9 ± 4.4	72.3 ± 4.8	75.5 ± 5.1	56.6 ± 5.0	57.9 ± 5.1	54.4 ± 5.4	<0.001
E/A	1.27 ± 0.09	1.26 ± 0.09	1.29 ± 0.08	1.30 ± 0.06	1.32 ± 0.07	1.37 ± 0.07	0.733
IVRT, ms	79.8 ± 5.0	69.3 ± 5.3	61.2 ± 5.6	81.0 ± 4.4	81.9 ± 4.9	77.6 ± 4.2	<0.001
IVCT, ms	95.8 ± 15.8	79.2 ± 12.9	78.1 ± 14.1	88.3 ± 9.6	87.8 ± 8.2	86.6 ± 9.1	0.015

Values are mean±SEM.

the decrease in E/A ratio and the increase in deceleration time, without implying a positive lusitropic effect of levosimendan in their studies. Furthermore, the well-known positive chronotropic effect of levosimendan[1] also might contribute to the decrease in E/A ratio seen in patients with heart failure because a negative linear relationship between heart rate and the E/A ratio has been described.[11,12]

In a recent Doppler echocardiographic study of patients with acute myocardial infarction, it was shown that 24-hour administration of levosimendan after primary angioplasty decreased the IVRT, which was interpreted as an improvement in diastolic function.[9] The E/A ratio increased to the same extent in both the levosimendan and placebo groups. Data on LV filling pressures were not presented, and no interventions were performed to maintain heart rate and cardiac loading conditions constant, making it difficult to distinguish the direct lusitropic effects of levosimendan from the chronotropic and vasodilatory effects of the drug on the Doppler echocardiographic variables. The pronounced increase in the E/A ratio in the placebo group after angioplasty suggests that the primary angioplasty procedure itself might have improved the diastolic function in these patients.

LV relaxation, an important element of diastolic function, is an energy-dependent process involving the removal of Ca^{2+} from troponin-C, followed by the dissociation of actin and myosin cross bridges, thus allowing the myofibrils to relax and to return to their original end-diastolic length.[14] LV relaxation is classically evaluated by the exponential time constant of isovolumic relaxation (τ), requiring cardiac catheterization to measure LV pressure. IVRT, a commonly used noninvasive variable of LV relaxation,[15] is regarded as a reflection of τ. Thus, a direct correlation between IVRT and τ has been described.[16–18] IVRT, however, is affected by both aortic[15] and left atrial pressures.[16] In an experimental study, Thomas et al[10] found that IVRT has a predictable quantitative relationship to τ and to left atrial and aortic pressures. IVRT was directly related to τ and aortic pressure and inversely related to left atrial pressure. In the present study, our goal was to study the potential direct effects of levosimendan on LV early relaxation, assessed by changes in IVRT. We therefore maintained aortic pressure and left atrial pressure at a constant level during the experimental procedure by colloid and vasopressor infusions. The evolution of arterial pressure and left atrial pressure was not significantly different between the 2 groups, suggesting that the 23% reduction in IVRT by the highest dose of levosimendan was caused by a more rapid isovolumic relaxation. Thus, in addition to the positive inotropic effect, levosimendan exerts a positive lusitropic effect in patients with LV hypertrophy and maintained systolic function.

IVRT is defined as the time distance between aortic valve closure (end systole) and mitral valve opening. One limitation of the present study was that aortic/LV end-systolic pressure was not measured. Instead, mean aortic pressure was used as a surrogate for LV end-systolic pressure and controlled by phenylephrine infusion. We therefore cannot completely exclude the possibility that LV end-systolic pressure might have been decreased by levosimendan, which to some extent could have contributed to the fall in IVRT.

Diastolic dysfunction with impaired LV relaxation and decreased LV chamber compliance is commonly seen in patients with severe aortic stenosis.[19] In addition, the ischemia-reperfusion injury after cardiac surgery and CPB might have further impaired diastolic function in the present study. Postoperatively and before drug administration, the transmitral blood flow velocity profile showed a "pseudonormalized pattern" with an E/A ratio >1, normal to moderately elevated E-dec time, and IVRT.[20,21] This, combined with higher-than-normal filling pressures and LV concentric hypertrophy with reduced LV end-diastolic dimensions,[22,23] indicates that a moderate stage of LV diastolic dysfunction with a decreased LV chamber compliance was present in our patients. Levosimendan, in contrast to placebo, shortened IVRT and decreased E-dec time and E-dec slope (made it steeper), most likely through a more rapid and pronounced LV relaxation, causing a shorter time for equilibration of left atrial and LV pressures and improved early filling of the LV. Filling of the
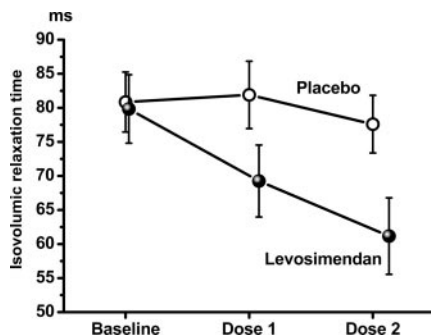

Figure 2. Effect of levosimendan vs placebo on IVRT (mean±SEM).

Table 5. Reproducibility of Doppler Echocardiographic Measurements

Variable	Bias	SD	Error	Upper Limit of Agreement	Lower Limit of Agreement
EDAI	−0.27	1.13	22.19	1.95	−2.49
ESAI	−0.02	0.63	22.10	1.21	−1.25
AEF	−0.01	0.05	23.83	0.09	−0.11
E-dec slope	−0.01	0.29	17.40	0.56	−0.57
E-dec time	2.49	19.67	16.16	41.05	−36.07
E-max	−0.01	0.06	16.16	41.05	−36.07
A-max	−0.01	0.05	14.06	0.08	−0.09
E/A	0.01	0.16	25.25	0.33	−0.31
IVRT	1.03	7.93	19.59	16.56	−14.50

LV in late diastole caused by atrial contraction (A-max) also was increased, which could be explained by a levosimendan-induced improved contractility of the left atrium. Despite the improved LV relaxation caused by levosimendan with improved LV filling, this positive lusitropic effect was not translated into an improvement in the LV end-diastolic pressure-area relationship. The LV end-diastolic area index was not increased with levosimendan compared with placebo at maintained LV filling pressures.

In light of the impaired relaxation seen in patients with LV hypertrophy, one would have expected that enhanced calcium sensitivity might have negative effects because increased sensitivity to calcium would further hinder relaxation of the heart, worsening diastolic dysfunction. Indeed, it has been shown that calcium sensitizers prolong relaxation time and impair diastolic function.[5,24] Levosimendan, on the other hand, does not prolong relaxation time.[25] Unlike other calcium sensitizers, levosimendan acts through direct binding with troponin-C, selectively increasing the affinity of troponin-C for calcium in a concentration-dependent manner.[26] It thus binds to troponin-C at high systolic intracellular calcium concentration and detaches from it at low diastolic concentration. An absence of calcium sensitization under low prevailing calcium concentrations during diastole would be of critical importance to prevent a worsening of heart failure. The mechanism responsible for the improvement of diastolic function, previously described in experimental in vitro studies[5,6] and demonstrated in the present study, is less understood. It has been shown that levosimendan also exerts a selective inhibition of phosphodiesterase-III activity, particularly in human myocytes,[27,28] which could explain the positive lusitropic effect, especially at higher concentrations.[29]

One could argue that the improved LV early filling seen with levosimendan could be caused by the generation of LV intraventricular restoring forces resulting from the levosimendan-induced increase in inotropy. It has been shown in animals with structurally normal hearts that when the LV contracts, the chamber may be compressed, generating restoring forces during systole, which allows filling to occur at lower-than-normal pressures.[30] Their magnitude is inversely related to the end-systolic volume and occurs at low LV end-diastolic pressures ($\approx$5 mm Hg).[30] We cannot completely rule out the possibility that the levosimendan-induced increase in LV filling is caused by the generation of restoring

forces, particularly because stroke volume and LV AEF increased with levosimendan. However, we consider this mechanism less likely because LV filling pressures (pulmonary capillary wedge pressure) were within the range of 12 to 15 mm Hg in both groups in the present study and because neither pulmonary capillary wedge pressure nor ESAI differed significantly between groups.

In a recent randomized controlled trial, Maslow et al[31] assessed the effects of epinephrine and milrinone on biventricular systolic and diastolic function after aortic valve replacement for aortic stenosis. According to their Doppler findings, both epinephrine and milrinone improved right and left ventricular function, whereas neither of the inotropic agents differed from placebo with respect to IVRT or early filling of the LV. The interpretation of their findings could be that milrinone and epinephrine have less obvious lusitropic effects in this situation, in contrast to the effects of levosimendan described in the present study, or that the potential beneficial effects of the epinephrine or milrinone on Doppler echocardiographic variables of LV diastolic function were obscured by the fact that no measures were taken to control heart rate or loading conditions in their study.

The use of inotropes or vasodilators to treat patients with aortic stenosis after aortic valve replacement is controversial because it may induce LV outflow obstruction.[32] Maslow et al[31] also evaluated the risk of LV outflow obstruction caused by epinephrine and milrinone stimulation and found no evidence of abnormal flow velocity profiles or LV outflow obstruction in any of the patients.[31] Their findings were confirmed by data from the present study showing no signs of levosimendan-induced LV outflow obstruction.

In this Doppler echocardiographic and hemodynamic study of patients undergoing valve replacement for aortic stenosis, we have shown that levosimendan shortens LV IVRT and improves LV filling early after valve replacement. We conclude that levosimendan, in addition to its inotropic effects, exerts a direct positive lusitropic effect in patients with LV hypertrophy.

Sources of Funding

Disclosures

None.

References

1. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, Hutchins S, Leier CV, LeJemtel TH, Loh E, Nicklas J, Ogilby D, Singh BN, Smith W. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure: Study Investigators. *Circulation*. 2000;102:2222–2227.
2. Lehmann A, Boldt J, Kirchner J. The role of Ca++-sensitizers for the treatment of heart failure. *Curr Opin Crit Care*. 2003;9:337–344.
3. McBride BF, White CM. Levosimendan: implications for clinicians. *J Clin Pharmacol*. 2003;43:1071–1081.
4. Grossman W. Diastolic function and heart failure: an overview. *Eur Heart J*. 1990;11(suppl C):2–7.
5. Hajjar RJ, Schmidt U, Helm P, Gwathmey JK. Ca++ sensitizers impair cardiac relaxation in failing human myocardium. *J Pharmacol Exp Ther*. 1997;280:247–254.

6. Janssen PM, Datz N, Zeitz O, Hasenfuss G. Levosimendan improves diastolic and systolic function in failing human myocardium. *Eur J Pharmacol*. 2000;404:191–199.

7. 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;128:2633–2639.

8. Parissis JT, Panou F, Farmakis D, Adamopoulos S, Filippatos G, Paraskevaidis I, Venetsanou K, Lekakis J, Kremastinos DT. Effects of levosimendan on markers of left ventricular diastolic function and neurohormonal activation in patients with advanced heart failure. *Am J Cardiol*. 2005;96:423–426.

9. De Luca L, Sardella G, Proietti P, Battagliese A, Benedetti G, Di Roma A, Fedele F. 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: 172–177.

10. Thomas JD, Flachskampf FA, Chen C, Guerrero JL, Picard MH, Levine RA, Weyman AE. Isovolumic relaxation time varies predictably with its time constant and aortic and left atrial pressures: implications for the noninvasive evaluation of ventricular relaxation. *Am Heart J*. 1992;124: 1305–1313.

11. Harrison MR, Clifton GD, Pennell AT, DeMaria AN. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. *Am J Cardiol*. 1991;67: 622–627.

12. Oniki T, Hashimoto Y, Shimizu S, Kakuta T, Yajima M, Numano F. Effect of increasing heart rate on Doppler indices of left ventricular performance in healthy men. *Br Heart J*. 1992;68:425–429.

13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.

14. Pagel PS, Grossman W, Haering JM, Warltier DC. Left ventricular diastolic function in the normal and diseased heart: perspectives for the anesthesiologist (1). *Anesthesiology*. 1993;79:836–854.

15. Lewis BS, Lewis N, Sapoznikov D, Gotsman MS. Isovolumic relaxation period in man. *Am Heart J*. 1980;100:490–499.

16. Myreng Y, Smiseth OA. Assessment of left ventricular relaxation by Doppler echocardiography: comparison of isovolumic relaxation time and transmitral flow velocities with time constant of isovolumic relaxation. *Circulation*. 1990;81:260–266.

17. Ochi H, Ikuma I, Toda H, Shimada T, Morioka S, Moriyama K. Isovolumic relaxation period as an index of left ventricular relaxation under different afterload conditions: comparison with the time constant of left ventricular pressure decay in the dog. *Jpn Circ J*. 1989;53:1521–1529.

18. Yellin EL, Hori M, Yoran C, Sonnenblick EH, Gabbay S, Frater RW. Left ventricular relaxation in the filling and nonfilling intact canine heart. *Am J Physiol*. 1986;250:H620–H629.

19. Sidebotham D, Merry A, Legget M. *Practical Perioperative Transoesophageal Echocardiography*. Edinburgh, UK: Butterworth-Heinemann; 2003.

20. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol*. 1998;32:865–875.

21. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 1997;10:246–270.

22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.

23. Skarvan K, Lambert A, Filipovic M, Seeberger M. Reference values for left ventricular function in subjects under general anaesthesia and controlled ventilation assessed by two-dimensional transoesophageal echocardiography. *Eur J Anaesthesiol*. 2001;18:713–722.

24. Hgashiyama A, Watkins MW, Chen Z, LeWinter MM. Effects of EMD 57033 on contraction and relaxation in isolated rabbit hearts. *Circulation*. 1995;9:3094–3104.

25. Haikala H, Nissinen E, Etemadzadeh E, Levijoki J, Linden IB. Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. *J Cardiovasc Pharmacol*. 1995;25:794–801.

26. Haikala H, Linden IB. Mechanisms of action of calcium-sensitizing drugs. *J Cardiovasc Pharmacol*. 1995;26(suppl 1):S10–S19.

27. Zimmermann N, Boknik P, Gams E, Herzig JW, Neumann J, Scholz H. Calcium sensitization as new principle of inotropic therapy in end-stage heart failure? *Eur J Cardiothorac Surg*. 1998;14:70–75.

28. Ajiro Y, Hagiwara N, Katsube Y, Sperelakis N, Kasanuki H. Levosimendan increases L-type Ca(2+) current via phosphodiesterase-3 inhibition in human cardiac myocytes. *Eur J Pharmacol*. 2002;435:27–33.

29. 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: 2141–2147.

30. LeWinter MM, Fabian J, Bell SP. Left ventricular restoring forces: modulation by heart rate and contractility. *Basic Res Cardiol*. 1998; 93(suppl 1):143–147.

31. Maslow AD, Regan MM, Schwartz C, Bert A, Singh A. Inotropes improve right heart function in patients undergoing aortic valve replacement for aortic stenosis. *Anesth Analg*. 2004;9:891–902.

32. Bartunek J, Sys SU, Rodrigues AC, van Schuerbeeck E, Mortier L, de Bruyne B. Abnormal systolic intraventricular flow velocities after valve replacement for aortic stenosis: mechanisms, predictive factors, and prognostic significance. *Circulation*. 1996;93:712–719.

CLINICAL PERSPECTIVE

Left ventricular (LV) systolic dysfunction often is accompanied by impaired LV relaxation, ie, diastolic dysfunction. Levosimendan enhances myocardial contractility through myofilament calcium sensitization and offers new therapeutic possibilities in patients with severe heart failure because of its combined inotropic and vasodilatory effects. The effects of levosimendan on diastolic function in humans, however, are not well understood, and results from recent studies on the effects of levosimendan on diastolic function in patients with severe heart failure and acute myocardial infarction are not conclusive. In the present randomized, blinded, placebo-controlled study, we evaluated the effects of levosimendan versus placebo on LV early relaxation in patients with LV hypertrophy and maintained systolic function in patients undergoing aortic valve surgery for severe aortic stenosis. LV performance, dimensions, and filling pattern, as well as systemic hemodynamics, were assessed by transesophageal 2-dimensional Doppler echocardiography and pulmonary artery catheterization. To circumvent the confounding effects of the levosimendan-induced hemodynamic changes on Doppler echocardiographic indexes of LV early relaxation, heart rate, preload, and afterload were kept constant by atrial pacing, by blood volume expansion with colloids, and by phenylephrine-induced vasoconstriction, respectively. We could demonstrate that levosimendan shortens LV isovolumic relaxation time and improves LV filling early after valve replacement. We conclude that levosimendan, in addition to its inotropic effects, exerts a direct positive lusitropic effect in patients with LV hypertrophy and diastolic dysfunction.

Circulation

Effects of Levosimendan on Left Ventricular Relaxation and Early Filling at Maintained Preload and Afterload Conditions After Aortic Valve Replacement for Aortic Stenosis

Kirsten Jörgensen, Odd Bech-Hanssen, Erik Houltz and Sven-Erik Ricksten

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/117/8/1075