Levosimendan Facilitates Weaning From Cardiopulmonary Bypass in Patients Undergoing Coronary Artery Bypass Grafting With Impaired Left Ventricular Function

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Background. **Levosimendan is a compound with vasodilatory and inotropic properties. Experimental data suggest effective reversal of stunning and cardioprotective properties.**

Methods. **This prospective, randomized, placebo-controlled, double-blind study included 60 patients with 3-vessel coronary disease and left ventricular ejection fraction (LVEF) of less than 0.50. Levosimendan administration (12 μg/kg bolus, followed by an infusion of 0.2 μg/kg/min) was started immediately after induction anesthesia. Predefined strict hemodynamic criteria were used to assess the success of weaning. If weaning was not successful, CPB was reinstituted and an epinephrine infusion was started. If the second weaning attempt failed, intraaortic balloon pumping (IABP) was instituted.**

Results. **The groups had comparable demographics. The mean (standard deviation) preoperative LVEF was 0.36 (0.8) in both groups. The baseline cardiac index was 1.8 (0.3) L/min/m^2 in the levosimendan group and 1.9 (0.4) L/min/m^2 in the placebo group. The mean duration of CPB to primary weaning attempt was 104 (25) minutes in the levosimendan and 109 (22) minutes in the placebo group. Primary weaning was successful in 22 patients (73%) in the levosimendan group and in 10 (33%) in the placebo group ($p = 0.002$). The odds ratio for failure in primary weaning was 0.182 (95% confidence interval, 0.060 to 0.552). Four patients in the placebo group failed the second weaning and underwent IABP compared with none in the levosimendan group ($p = 0.112$).**

Conclusions. **Levosimendan significantly enhanced primary weaning from CPB compared with placebo in patients undergoing 3-vessel on-pump coronary artery bypass grafting. The need for additional inotropic or mechanical therapy was decreased.**

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Most patients with uncompromised preoperative heart function can be weaned from cardiopulmonary bypass (CPB) without inotropic agents [1]. However, in patients with preoperatively impaired ventricular function, weaning failure without medical or mechanical support may be seen in up to 70% to 80% [2–4].

Complicated weaning may lead to myocardial distension and damage, end-organ failure due to impaired perfusion, neurologic complications, increased operative room times, and need for multiple medications and mechanical support.

Traditional positive inotropic agents improve contractility by increasing intracellular concentrations of free calcium, either by increasing the intracellular concentrations of cyclic adenosine monophosphate (cAMP) by β-adrenergic stimulation (epinephrine, dobutamine, dopamine), or by blocking the degradation of cAMP (mil-

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rinone). However, contractility with these agents is increased at the expense of increased myocardial energy consumption, risk of ischemia, and arrhythmias [5].

Levosimendan does not increase the concentration of intracellular calcium. Instead, it induces a calcium-dependent conformational change of troponin C and enhances the rate and extent of contraction of cardiac myofilaments during systole [6]. Levosimendan increases cardiac output without increasing myocardial oxygen consumption in patients early after CPB for coronary artery bypass grafting (CABG) [7, 8]. It also exerts vasodilatory and possible antiischemic and cardioprotective effects by opening of the adenosine triphosphate-dependent potassium (K_{ATP})-channel [9–11].

This study was designed to explore the effect of prophylactic levosimendan administration on weaning from and early recovery after CPB in patients with preoperatively impaired left ventricular function undergoing CABG.

Patients and Methods

The study was a randomized, double-blind, and placebo-controlled phase II study performed in 2 university centers. Sixty patients undergoing on-pump CABG were enrolled, and randomization was performed using permutated blocks and stratified by center. The study protocol was approved by the Ethical Committees of the hospitals, and all patients enrolled gave their written informed consent before screening.

The main criteria for inclusion were 3-vessel coronary artery disease, impaired left ventricular ejection fraction (LVEF $\leq$ 0.50 evaluated with left ventricular cineangiography or echocardiography $\leq$ 3 months before inclusion), or signs of acute ischemic congestive heart failure (CHF), or both. The main exclusion criteria were previous CABG, indication for any cardiac valve operation, weight exceeding 160 kg, severe chronic obstructive pulmonary disease, and administration of levosimendan within the preceding 30 days.

Anesthesia was performed using a standardized, protocol-specified regimen of intravenous agents (propofol, sufentanil, rocuronium). Ephedrine was allowed as a vasopressor during anesthesia induction and phenylephrine or vasopressin thereafter during the operation and during the weaning procedure to maintain mean arterial pressure of 60 mm Hg or higher. After intubation, a fiberoptic pulmonary artery catheter was inserted through the right internal jugular vein.

Ringer's solution was infused at 40 to 60 mL/h and additional fluid was given, if needed, to maintain pulmonary artery capillary wedge pressure (PCWP) at 10 to 12 mm Hg or at the baseline value. After completion of baseline hemodynamic measurements, levosimendan or a corresponding placebo infusion was started. A bolus dose of 12 μg/kg of levosimendan during a 10-minute interval was followed by a continuous infusion of 0.2 μg/kg/min for a total infusion period of 24 hours. Placebo was supplied in identical packaging to levosimendan, including a coloring agent to achieve a similar color to the levosimendan solution, and was diluted and infused according to an identical schedule to levosimendan.

A CPB circuit with a membrane oxygenator (Dideco Avant, Mirandola, Italy, or Affinity, Medtronic, Brooklyn Park, MN) was primed with 1500 to 2000 mL of Ringer's solution and 100 mL of 15% mannitol. A nonpulsatile flow of 2.4 L/min/m^2 or more, Pa_{O_2} exceeding 30 kPa, and hematocrit of 22 or higher were provided to maintain mixed venous oxygen saturation (SVO_2) of 70%. Perfusion pressure was kept between 60 to 80 mm Hg. Mechanical ventilation of the lungs was stopped during CPB, and Pa_{CO_2} was kept at 5 to 6 kPa by adjusting the fresh gas flow through the oxygenator. Blood glucose level was maintained between 4 to 8 mmol/L with short-acting insulin.

In all subjects, aortic cross-clamping with cold blood cardioplegia was used. The nasopharyngeal temperature was allowed to decrease during perfusion to 32° to 33°C. Active warming (bladder temperature $\geq$ 35.5°C and nasopharyngeal temperature $<$ 37°C) was started 15 to 20 minutes before the anticipated removal of the aortic cross-clamp.

After the aorta was declamped, the heart was defibrillated, if necessary, and rescue medication (magnesium, lidocaine, amiodarone) was used, at the discretion of the investigator. Epicardial, preferably atrial, pacing to achieve a moderately elevated heart rate (80 to 88 beats/min) was used.

Criteria for attempting weaning consisted of reperfusion time of one-third or more of the aortic cross-clamp time, perfusion pressure exceeding 60 mm Hg at a pump flow of 2.4 L/m^2/min; absence of acidosis (pH $<$ 7.3 and base excess $<$ −3); serum potassium, 5 to 6 mmol/L; and bladder temperature, 35.5°C or higher.

The subjects were weaned from the CPB gradually, keeping central venous pressure (CVP) at 6 to 8 mm Hg and SVO_2 exceeding 60% while reducing the pump flow. At the end of the weaning procedure, CVP was allowed to be increased to a level of 12 mm Hg and PCWP to a level of 16 mm Hg, if indicated.

There were four criteria for successful weaning, assessed at 10 minutes after cessation of bypass:

1. Cardiac index (CI), 2.2 L/m^2/min or higher;
2. SVO_2, 70% or higher;
3. CVP, 12 mm Hg or less;
4. PCWP, 16 mm Hg or less.

All criteria were to be met to claim successful weaning. If weaning was claimed successful, administration of protamine and decannulation were started.

If weaning failed, CPB was restarted and an epinephrine infusion of 0.10 μg/kg/min was started. Weaning was reattempted after 10 minutes. If the second weaning attempt failed, CPB was again resumed and an intraaortic balloon pump (IABP) was inserted.

If CI decreased 2.2 L/m^2 or more and SVO_2 decreased 65% or more after weaning, rescue inotropic medication (ephedrine, epinephrine, or milrinone) was administered. After the operation was completed, propofol was

Table 1. Baseline Data and Demographics of the Patients

Variable, mean ± SD or No.	Levosimendan (n = 30)	Placebo (n = 30)	*p* Value[a]
Age, year	64 ± 10	64 ± 10	0.851
Male	28	26	0.389
BMI, kg/m^2	29 ± 5	27 ± 4	0.289
Severity of CAD			
3-vessel disease	30	30	1.000
Previous MI	26	25	1.000
Previous PCI	2	2	1.000
Acute MI	6	3	0.472
Unstable angina	1	2	1.000
Diabetes	13	10	0.596
Hypertension	18	22	0.412
Medication			
β-Blocker	28	28	1.000
ACE inhibitor	16	17	1.000
Lipid-modifying agent	26	25	1.000
Antithrombotic agent	24	17	0.095
NYHA class			
II	4	6	0.772
III	20	19	
IV	6	5	
EuroSCORE	5 ± 3	5 ± 3	0.819
Pre-op LVEF	0.36 ± 0.08	0.36 ± 0.08	0.838
Pre-op LVEF			
≤0.30	9	11	0.407
>0.30 to ≤ 0.40	15	10	
>0.40 to ≤ 0.50	6	9	
Baseline CI in L/min/m^2	1.8 ± 0.3	1.9 ± 0.4	0.555
Duration of operation, min	245 ± 51	255 ± 46	0.466
Perfusion time before first weaning, min	104 ± 25	109 ± 22	0.457

[a] Two-group *t* test and Fisher exact test were used for continuous and categoric variables, respectively.

ACE = angiotensin converting enzyme; CAD = coronary artery disease; CI = cardiac index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SD = standard deviation; PCI = percutaneous coronary intervention.

continued at a sedative dose and phenylephrine infusion, if ongoing, was converted to norepinephrine.

Management of patients in the intensive care unit (ICU) was in accordance with institutional guidelines. Each patient was discharged from the ICU at the discretion of the intensive care specialist.

End Points

The primary end point of the study was the proportion of patients successfully weaned from CPB by the first attempt (criteria given in the previous section). Other variables studied included invasive hemodynamic measurements, need for vasoactive medication, 24-hour fluid balance, myocardial markers, pharmacokinetics, postoperative recovery, and safety data up to 31 days.

Statistical Methods

Sample size estimation was based on the assumptions that (1) 65% of placebo-treated patients fail at primary weaning and that (2) perioperative levosimendan would decrease weaning failures to 30%. With a total of 60 subjects, the two-sided χ^2 square test (nQuery Advisor 4.0, Statistical Solutions, Saugus, MA) had 80% power to detect treatment effect at nominal $\alpha = 0.05$ level.

The primary efficacy variable was analyzed using stratified Cochran-Mantel-Haenszel test controlling for study center. The Mantel-Haenszel odds ratio for failure and corresponding 95% confidence interval were reported.

Similarities of baseline characteristics were statistically evaluated using two-group *t* test and the Fisher exact test for continuous and categoric variables, respectively. The continuous variables were compared between the two study groups using repeated-measures analysis of variance (ANOVA) model with effects for treatment, time point, and treatment–time point interaction. Significance of treatment effect was also evaluated at each time point separately using ANOVA contrasts for same model.

Markers for myocardial injury and natriuretic peptides violated the normality assumption for the ANOVA test. Therefore, the nonparametric Friedman test was applied.

Time to start of rescue medication, and other time-to-event type of end points were analyzed using Cox proportional hazards model with effects for treatment. Cumulative doses of selected medications were compared between treatment groups using the Mann-Whitney test (M-W).

Results

Baseline data and demographics are presented in Table 1. Altogether, 30 patients received levosimendan (21 in center 1, and 9 in center 2) and 30 received placebo (21 in center 1, and 9 in center 2). The groups were comparable

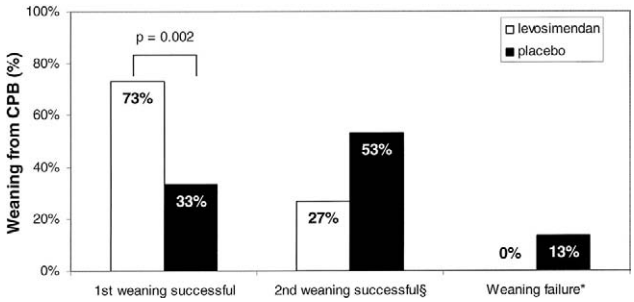

*Fig 1. Weaning from cardiopulmonary bypass (CPB). First weaning attempt with levosimendan and placebo. Epinephrine added to second weaning attempt. §Two levosimendan patients were weaned in primary attempt although failed to meet primary endpoint hemodynamic criteria. *Weaning failure leads to use of intra-aortic balloon pump.*

Table 2. Hemodynamic Variables and Mixed Venous Oxygen Saturation

Variable				After Declamping Aorta			*p* Value[a] for		
Mean ± SD	Group	Baseline	End of Surgery	4 hours	8 hours	24 hours	Treatment	Time	Interaction
HR, bpm	LS	53 ± 10	88 ± 15.4	93 ± 10.6[b]	96 ± 10.8	91 ± 14.3	0.047	0.005	0.639
	PL	57 ± 14	87 ± 13.4	86 ± 9.7	93 ± 14.9	88 ± 12.7			
MAP, mm Hg	LS	74 ± 15	65 ± 9.4	68 ± 10.1	68 ± 9.9	73 ± 10.1	0.215	0.002	0.531
	PL	77 ± 14	73 ± 10.5	78 ± 12.4	74 ± 9.9	80 ± 12.9			
CVP, mm Hg	LS	8.0 ± 3.3	10.3 ± 3.0	9.5 ± 2.7	10.6 ± 6.1	9.5 ± 4.0	0.795	0.143	0.944
	PL	8.0 ± 2.4	11.1 ± 2.4	9.2 ± 2.9	10.3 ± 3.8	9.2 ± 3.3			
MPAP, mm Hg	LS	18 ± 5	22 ± 4.7	23 ± 4.9	24 ± 6.0	22 ± 4.6	0.666	0.005	0.557
	PL	19 ± 5	23 ± 6.8	24 ± 5.8	25 ± 5.9	23 ± 4.8			
PCWP, mm Hg	LS	11 ± 4	12 ± 3.2	11 ± 3.0	12 ± 4.4	12 ± 3.2	0.721	0.097	0.554
	PL	11 ± 4	13 ± 2.8	12 ± 4.0	12 ± 3.3	13 ± 4.0			
SVRI, dyne · sec/cm^5	LS	11 ± 4	7.3 ± 2.4	6.3 ± 2.1	6.2 ± 2.3	6.9 ± 2.8	0.645	0.006	0.64
	PL	12 ± 5	9.4 ± 3.2	8.1 ± 2.8	7.6 ± 2.0	8.2 ± 2.9			
PVRI, dyne · sec/cm^5	LS	2.6 ± 0.7	2.4 ± 0.7	2.1 ± 0.8	2.3 ± 1.3	2.2 ± 1.0	0.909	0.054	0.821
	PL	2.6 ± 1.0	2.9 ± 1.1	2.5 ± 0.9	2.5 ± 0.8	2.3 ± 0.7			
SV, mL/bpm	LS	69 ± 14	56 ± 15.9	64 ± 15.7	63 ± 15.3	65 ± 15.3	0.781	0.157	0.701
	PL	67 ± 16	51 ± 15.1	62 ± 17.0	57 ± 13.3	62 ± 13.6			
LVSWI, g · m/m^2	LS	3743 ± 1086	2723 ± 968	3378 ± 910	3454 ± 825	3800 ± 988	0.663	0.02	0.665
	PL	3872 ± 1063	2773 ± 933	3641 ± 1198	3302 ± 1161	3808 ± 908			
SVO_2, %	LS	72 ± 7.5	74 ± 7.2	68 ± 6.4	66 ± 6.7	65 ± 8.2	0.403	<0.001	0.32
	PL	73 ± 6.9	73 ± 10.3	68 ± 8.0	64 ± 6.1	61 ± 6.0			

[a] Repeated measures analysis of variance to compare levosimendan (LS) with placebo (PL) has been calculated for change from baseline to 4 to 24 hours after declamping aorta. [b] Statistically significant difference between levosimendan and placebo at the visit.

CVP = central venous pressure; HR = heart rate; LVSWI = left ventricle stroke volume index; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; SD = standard deviation; SV = stroke volume; SVO_2 = mixed venous oxygen saturation; SVRI = stroke volume index.

in cardiovascular history, indication for CABG, preoperative ejection fraction, or signs of acute ischemic CHF.

Primary End Point

Primary weaning was successful in 22 of 30 subjects in the levosimendan group and in 10 of 30 subjects in the placebo group. The odds ratio for the weaning failure in the primary attempt was 0.182 (95% confidence interval, 0.060 to 0.552; $p = 0.002$).

No patient in the levosimendan group, but 4 in the placebo group failed the second weaning attempt and underwent IABP (Fisher exact test, $p = 0.112$; Fig 1).

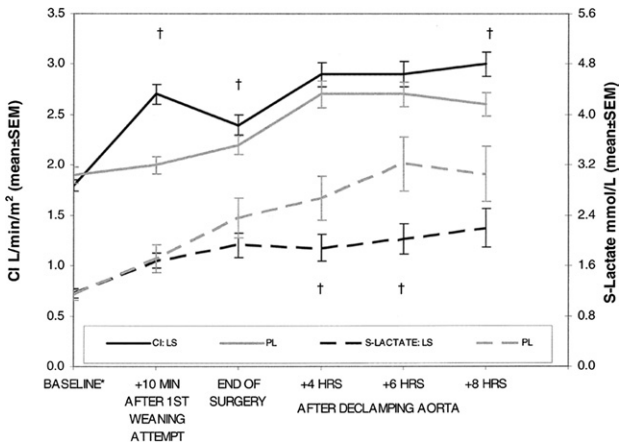

Fig 2. Cardiac index (CI) and lactate values in levosimendan (black lines) and placebo (gray lines) groups. Baseline denotes after induction of anesthesia. (†Denotes $p < 0.05$ between levosimendan and placebo.)

Hemodynamic Variables

Hemodynamic data are summarized in Table 2. The mean heart rate at baseline was higher in the placebo group compared with levosimendan group, with mean values of 57 and 53 beats/min, respectively. In contrast, at 4, 6, 8, and 12 hours after declamping the aorta, the recorded heart rate was higher in the levosimendan group, and a statistically significant difference was detected between the treatment groups in heart rate over time ($p = 0.047$).

The CI values at baseline were similar in both groups, with mean values of 1.8 and 1.9 L/min/m^2 for the levosimendan and placebo groups, respectively. CI increased at the end of the operation and at 4, 6, 8, 12, and 25 hours after declamping the aorta in both groups compared with the baseline (Fig 2).

Vasoactive Medication

Epinephrine was started at weaning in 8 patients in the levosimendan group and in 20 placebo-treated patients. The use of inotropic medications early after CPB is indicated in Table 3. During postweaning recovery, epi-

Table 3. Use of Rescue Inotropic Medications Within 6 Hours After Declamping Aorta

Drug	Levosimendan (n = 30)	Placebo (n = 30)
Epinephrine		
Patients, No. (%)	15 (50.0)	24 (80.0)
Cumulative dose, median (range), mg	2.2 (0.3–5.2)	1.8 (0.0–3.1)
Milrinone		
No. (%)	2 (6.7)	5 (16.7)
Cumulative dose, median (range), mg	7.6 (4.5 - 10.7)	6.9 (2.0–9.2)

nephrine was started in 11 patients in the levosimendan group compared with 6 patients in the placebo group.

Vasopressors were given to all patients in the levosimendan group and to 28 patients in the placebo group. During the operation, hypotension was treated with phenylephrine and was administered to 27 patients in the levosimendan group and to 26 patients in the placebo group. Cumulative doses of phenylephrine were significantly higher in the levosimendan group: median (interquartile range [IQR]) 14 mg (10 to 20 mg) in the levosimendan group and 5 mg (1 to 13 mg) in the placebo group (M-W, $p < 0.001$).

In the ICU, hypotension was treated with norepinephrine in 27 patients in the levosimendan group and 22 patients in the placebo group. The median (IQR) cumulative dose of norepinephrine was 12 mg (8 to 25 mg) in the levosimendan group and 13 mg (8 to 21 mg) in the placebo group (M-W, $p = 0.755$). Vasopressin was administered to 2 patients in the levosimendan group (cumulative doses of 19 and 66 mg) and to 1 patient in the placebo group (cumulative dose of 106 mg).

The 24-Hour Fluid Balance

No significant difference was detected between the treatment groups in fluid input, output, and fluid balance.

Markers of Myocardial Injury

After operation, N-terminal proatrial natriuretic peptide (NT-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) increased in both groups without any significant difference between the groups.

There were no significant differences between the groups in the changes in P-creatine kinase-MB subunit (P-CK-MB). However, P-troponin T increased statistically significantly more in the placebo group than in the levosimendan group. The median (IRQ) P-troponin T concentration in μg/L was 0.03 (0.03 to 0.03) in both groups at baseline, 0.22 (0.16 to 0.41) in the levosimendan group and 0.37 (0.23 to 0.59) in the placebo group at the end of the procedure; 0.33 (0.26 to 0.91) and 0.69 (0.39 to 1.32) at 24 hours, and 0.23 (0.18 to 0.52) and 0.51 (0.29 to 0.81), respectively, at 2 days ($p = 0.037$). One patient in the levosimendan group and 3 patients in the placebo group had postoperative P-CK-MB levels that exceeded 100 μg/L.

Serum Lactate

The mean lactate value increased significantly more from baseline in the placebo group compared with the levosimendan group at 4 hours ($p = 0.004$) and at 6 hours ($p = 0.015$) after the aorta was declamped. The increase in lactate was also significantly higher in the placebo group than in the levosimendan group during the 4- to 24-hour period after aortic declamping (Fig 2).

Postoperative serum lactate levels exceeding 3 mmol/L were measured in 9 patients in the levosimendan group and in 15 patients in the placebo group. Postoperative serum lactate exceeding 6 mmol/L was measured in 2 patients in the levosimendan and 5 patients in the placebo group.

Pharmacokinetics

Levosimendan was rapidly absorbed and eliminated from plasma after the end of the study drug infusion. The mean ± SD peak concentration 98 ± 33 ng/mL was reached approximately 2 hours after the start of the study drug infusion. The mean half-life of elimination was 1.3 ± 0.4 hours. The active metabolites of levosimendan were formed slowly after the study drug infusion. The mean peak concentration of OR-1855 (6.6 ± 4.9 ng/mL) and OR-1896 (7.7 ± 6.3 ng/mL) were reached approximately 140 hours (6 days) after the start of the infusion.

Postoperative Recovery

The patients were extubated in a median (range) of 21 (10 to 792) hours in the levosimendan group compared with 23 (10 to 580) hours in the placebo group (Cox, $p = 0.567$). The median (range) duration of stay in the ICU was 2 (1 to 33) days in the levosimendan group and 2 (1 to 31) days in the placebo group (Cox, $p = 0.658$). The median for days alive and out of hospital for 31 days were 20 days in both groups. Two patients, both from the placebo group, died during the study period of ventricular fibrillation and multiorgan failure.

Comment

The results of this prospective randomized study indicate that in patients with impaired systolic heart function, the use of prophylactic levosimendan significantly increases the probability of successful weaning from CPB compared with placebo.

Levosimendan may facilitate weaning from CPB by both its inotropic and lusitropic properties. The direct inotropic effects have been demonstrated by intracoronary injections of levosimendan in failing human hearts [12]. Lusitropic effects of levosimendan (ie, improvement of left ventricular relaxation and filling) have been shown in patients with left ventricular hypertrophy due to aortic stenosis [13]. However, the methods used in this study do not allow identification of the mechanisms involved in improving myocardial performance observed during and after weaning from CPB in patients receiving levosimendan.

After CPB and ischemic cardioplegic arrest, the systolic performance of the heart is invariably depressed by

postischemic stunning [14]. Stunning may easily be reversed by standard inotropic agents. Their basic mechanism of inotropic action is an increase in intracellular calcium. The associated increase in myocardial oxygen consumption may be harmful and may provoke ischemia, apoptosis, and cell death [15]. Levosimendan also reverses stunning effectively but it does not increase intracellular calcium [16, 17].

Levosimendan is suggested to exert cardioprotective effects by activation of K_{ATP} channels [11,18, 19]. We used total intravenous anesthesia to exclude the interference of inhalational anesthetics on the K_{ATP} channels [20]. Interestingly, the increase in postoperative P-troponin T was significantly smaller in the levosimendan group than in the placebo group in our study. Earlier an attenuation of P-troponin I release has been demonstrated in a small study in patients undergoing on-pump CABG receiving levosimendan pretreatment [19].

A few previous studies and case series suggest that levosimendan improves cardiac performance and loading conditions after CPB [21–26]. These studies may implicate an adjunctive role of levosimendan with other cardiac medications, as has been suggested for nesiritide [27].

In a recent study in cardiac surgical patients with a low preoperative ejection fraction, stroke volume was better maintained with the combination of dobutamine and levosimendan than with the combination of dobutamine and milrinone [28]. We showed the effects by performing a placebo-controlled study with levosimendan.

In the present study, the changes of hemodynamic variables after weaning from CPB were largely comparable in the two study groups. However, the prompt use of concomitant treatments to maintain hemodynamic parameters within predetermined limits probably influenced these changes: rescue inotropic medication was given to 63% of the patients in the levosimendan and to 87% of the patients in the placebo group, and PCWP and CVP were targeted to predetermined levels with fluid therapy according to the study protocol.

Still, cumulative phenylephrine requirements to counteract hypotension were higher in the levosimendan group during anesthesia and CPB, and both systemic and pulmonary vascular resistances and also systolic pulmonary artery pressure decreased significantly more over time in the levosimendan group. Levosimendan is known to act on the K_{ATP} channels of the peripheral resistance vessels, leading to vasodilation and eventually also hypotension, which might be a problem in vasodilatory conditions such as CPB. In the present study, however, hypotension was easily controlled with phenylephrine and norepinephrine. In the study by Lilleberg and colleagues [29], levosimendan decreased blood pressure and increased heart rate in heart failure patients, as was the case in the present study.

Interestingly, lactate levels were lower in the levosimendan-treated patients in our study, which may reflect improved tissue oxygenation. Lactate may be a relevant prognostic marker for outcome, because using lactate levels of less than 2 mmol/L as a goal to direct hemodynamic optimization in postoperative cardiac patients resulted in a shorter ICU stay and less organ damage [30]. We acknowledge, though, that the use of epinephrine may have influenced the lactate levels.

The plasma levels of the active levosimendan metabolites peaked at 6 days instead of the previously observed 2 to 4 days in the heart failure population [29]. The reason for this altered formation of the metabolites may be related to the use of prophylactic broad-spectrum antibiotics and a consequently diminished amount of intestinal bacteria, which are known to be essential for the formation of the metabolites [31].

Considering the potential clinical effect of our study, the main limitation is that it did not have an active control. Today, most cardiac surgical centers would use milrinone when problems in weaning from CPB are anticipated. Milrinone and other phosphodiesterase inhibitors have been shown to be efficacious for this purpose [1–3]. In experimental studies, however, milrinone increased myocardial oxygen consumption significantly more than levosimendan in equipotent doses [32, 33].

The criteria used for CPB weaning in the present study were more stringent compared with everyday practice and may have resulted in high epinephrine requirements in our patients. However, the criteria were objective and allowed rigorous comparison of the primary efficacy variable between the groups.

Despite the beneficial effect of levosimendan on the primary efficacy variable, no statistically significant differences were detected between the treatment groups in duration of stay in the ICU or the duration of hospitalization or death. In an unblinded study, the combination of dobutamine and levosimendan was associated with shorter intubation time than the combination of dobutamine and milrinone in patients with poor ventricular function after CPB [28]. However, the present study was planned and powered to detect a difference in the primary variable, which was weaning from CPB.

In conclusion, the present randomized, controlled study shows that prophylactic levosimendan facilitates weaning from CPB in patients with impaired preoperative left ventricular function undergoing CABG. However, studies designed and powered to detect relevant clinical outcomes are needed before justifiable practice advisories regarding its use in cardiac surgery can be made.

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