British Journal of Anaesthesia **106** (3): 298–304 (2011)
Advance Access publication 21 January 2011 · doi:10.1093/bja/aeq402

BJA

CARDIOVASCULAR

Preoperative levosimendan infusion in combined aortic valve and coronary bypass surgery

H. Leppikangas[1]*, K. Järvelä[2], T. Sisto[2], P. Maaranen[2], M. Virtanen[2], P. Lehto[2], S. Karlsson[3], T. Kööbi[4] and L. Lindgren[1]

[1] Department of Anaesthesia, Tampere University Hospital, [2] Heart Center, Tampere University Hospital, [3] Department of Intensive Care, Tampere University Hospital, and [4] Deparment of Clinical Physiology, Tampere University Hospital, PO Box 2000, Tampere 33521, Finland

* Corresponding author. E-mail: heli.leppikangas@pshp.fi

Editor's key points

- Levosimendan is an inodilator.
- The aim was to see whether this drug, given before operation, offered any benefits in high-risk cardiac surgery.
- After operation, patients in the levosimendan group maintained higher cardiac index and stroke volume than the control group.
- Levosimendan improved perioperative haemodynamics in patients undergoing high-risk cardiac surgery.

Background. Cardiopulmonary bypass may have detrimental effects on intestinal function and decrease the concentrations of the active, long-acting metabolites of levosimendan, an inodilator used to improve cardiac function. The aim of this study was to evaluate the haemodynamic effects of preoperative levosimendan in patients undergoing high-risk cardiac surgery.

Methods. Twenty-four patients were randomized to receive levosimendan (12 μg bolus followed by an infusion of 0.2 μg kg^{-1} min^{-1}) or a placebo 24 h before surgery. The inclusion criteria were left ventricular ejection fraction (LVEF) $<$50% or LV hypertrophy indicated by a wall thickness of $>$12 mm. Haemodynamics were recorded every hour for 24 h (pulmonary artery catheter) and daily until postoperative day 4 (whole-body impedance cardiography). Doppler echocardiography with tissue Doppler imaging was used to assess systolic and diastolic cardiac function.

Results. The cardiac index (CI) and stroke volume index (SI) were higher in the levosimendan group (LG) for the 4 day postoperative period ($P<0.05$); on the fourth postoperative day, the CI was 3.0 litre m^{-2} min^{-1} in the LG compared with 2.4 litre m^{-2} min^{-1} in the control group (CG) and the SI was 30 *vs* 25 ml m^{-2}, respectively. The LVEF measured at baseline and on the fourth postoperative morning decreased in the CG, but was maintained in the LG.

Conclusions. Levosimendan improved haemodynamics compared with a placebo in patients undergoing high-risk cardiac surgery. The concentrations of levosimendan's metabolites were higher compared with earlier studies using perioperative dosing.
URL: https://register.clinicaltrials.gov
ClinicalTrials.gov Identifier: NCT01210976

Keywords: heart, coronary artery bypass; heart, inotropism; surgery, cardiovascular

Accepted for publication: 3 December 2010

Patients undergoing aortic valve replacement (AVR) surgery combined with coronary artery bypass grafting (CABG) are at risk for left ventricular (LV) dysfunction.[1] Vasoactive therapy could be required for weaning from cardiopulmonary bypass (CPB) or to increase tissue perfusion in the perioperative period.[2] Maintaining adequate cardiovascular function is essential for sufficient oxygen delivery. Adequate oxygen delivery and normal mixed venous saturation (Sv_{O_2}) values during the immediate postoperative period after cardiac surgery can decrease morbidity and, therefore, reduce the length of the hospital stay.[3] Levosimendan, a calcium-sensitizing inodilator, enhances myocardial contractility and causes both coronary and peripheral vasodilatation[4] without increasing the myocardial oxygen demand.[5] Levosimendan is used to improve cardiac function and was used in patients suffering from congestive heart failure,[6] before and after operation after CABG,[7 8] and for patients in septic shock.[9]

Levosimendan has an intermediate metabolite OR-1855, which is further acetylated to the active metabolite OR-1896. It is formed by intestinal bacteria and its half-life is 77 (9) h.[10] The metabolite OR-1896 has haemodynamic and pharmacological properties similar to the parent drug.[11 12] CPB is associated with an imbalance in oxygen demand and supply in the hepatosplanchnic region,[13] which may have detrimental effects on intestinal function. Patients infused with levosimendan during the perioperative period may lack the active metabolite. Our aim was to infuse levosimendan on the day before surgery to ensure the presence of OR-1896. Here, we describe the haemodynamic effects of levosimendan, compared with a placebo, in patients undergoing AVR together with CABG.

Methods

Twenty-four patients undergoing AVR with CABG were enrolled in the study. The inclusion criteria were LV ejection fraction (LVEF) $<$50% or LV hypertrophy, as indicated by a wall thickness of $>$12 mm. The exclusion criterion was a known allergy to levosimendan. The ethics committee of the hospital approved the study protocol and it was registered with EudraCT (ref: 2008-001672-70). Written informed consent was obtained from all patients before enrolling. The same surgical team performed all the operations (T.S., P.M., and K.J.).

The patients were randomized (sealed opaque envelopes) into two groups: the levosimendan group (LG) and the control group (CG). A study nurse prepared and diluted the study drugs, thereby ensuring that all personnel were blinded to the group assignment. Infusion of the study drug started the day before surgery. In the LG, patients received a levosimendan (Simdax®; Orion Pharma, Espoo, Finland) bolus 12 μg kg^{-1} in 10 min followed by a 24 h infusion at a rate of 0.2 μg kg^{-1} min^{-1}. In the CG, patients received a placebo bolus and infusion, which were made to look identical to levosimendan with water-soluble vitamin concentrate (Soluvit®; Fresenius Kabi, Uppsala, Sweden, 10 ml diluted in 500 ml of glucose 5%).

The anaesthesia and CPB were performed according to the hospital's clinical practice. A pulmonary artery catheter (Criticath SP5537; Becton Dickinson, Singapore) was inserted for haemodynamic monitoring in the operating theatre.

At admission to the operating theatre and thereafter, the goals and means of haemodynamic support were to keep the pulmonary capillary wedge pressure (PCWP) at the level of 12–18 mm Hg with fluid administration, the mean arterial pressure between 60 and 90 mm Hg with the aid of norepinephrine or sodium nitroprusside, and the cardiac index (CI) above 1.8 litre min^{-1} m^{-2} with dobutamine. If the CI was still $<$1.8 litre min^{-1} m^{-2}, milrinone or epinephrine was added.

Haemodynamic measurements were made before and after induction of anaesthesia, after weaning from perfusion, after sternum closure, at admission to the intensive care unit (ICU), and hourly thereafter for 24 h. Blood gases and mixed venous saturation, lactate, and haematocrit were taken according to the same schedule, except at 4 h intervals in the ICU. Levosimendan, OR-1896, and OR-1855 concentrations were measured at baseline, before induction of anaesthesia, and at 72 and 96 h. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was taken at baseline, before induction of anaesthesia, and on the fourth postoperative morning. P-creatine kinase (P-CK) and P-creatine kinase-MB subunit (P-CK-MB) were taken 6 h after operation and on the first and second postoperative mornings.

Whole-body impedance cardiography

CircMon B202 (JR Medical Ltd, Tallinn, Estonia) was used for the measurement of whole-body impedance cardiography (ICG_{WB})-derived stroke volume index (SI), heart rate (HR), CI, left cardiac work index (LCWI), systemic vascular resistance index (SVRI), and extracellular water (ECW). This method is described in detail elsewhere.[14] Disposable electrocardiogram electrodes (Blue sensor type R-00-S/25, Ambu®, Denmark) were used. A pair of electrically connected current electrodes was placed on distal parts of the extremities, immediately proximal to the wrists and ankles. Voltage electrodes were placed proximal to the current electrodes; the distance between the electrodes was 5 cm. Measurements were done in the supine position, and the patient's limbs were isolated from the trunk to prevent an electric connection during the bioimpedance measurements. ECW[14] was calculated using the equation: $ECW = K*H^2/R$, where H was the patient's height (cm), R the resistive part of the whole-body bioimpedance (Ω), and K the correction factor ($K_{males}=0.078$, $K_{females}=0.095$). Arterial blood pressure was measured non-invasively using Accutorr 4 (DatascopeCorp, Montvale, NJ, USA).

After baseline measurements, the study drug infusion was started. On the morning of surgery, the ICG_{WB} measurements were done before the patients received their scheduled medications. Postoperative measurements were performed on the first and fourth postoperative mornings.

Echocardiography

Transthoracic echocardiography was performed by the same cardiologists (M.V. and P.L.) at baseline and on the first and fourth postoperative days. An Esaote Mylab 30CV (ESAOTE S.p.A, Firenze, Italy) was used for standard measurements. The LVEF was measured from the two-dimensional echocardiography using biplane Simpson's method. The M-mode was used to measure the LV mass and conventional cardiac dimensions. The mitral and aortic flow patterns were recorded with Doppler echocardiography and the mitral annular velocities with tissue Doppler imaging. Systolic pulmonary pressure was estimated non-invasively by adding the peak gradient of tricuspid regurgitation to the right atrial pressure estimated from the dimensions of the inferior vena cava and its decrease on deep inspiration.

Statistical methods

We calculated the sample size based on published data.[15] Sample size was estimated as 10 patients per group, with a two-sided α level of 0.05 and a power of 0.80 to detect a 7.5 ml m^{-2} difference in SI, with an SD of 5, at the end of study. We decided to enrol 12 patients in each group in the case of drop outs. Baseline variables were tested using Student's t-test and Fisher's exact test for continuous and categorical variables, respectively. Normally distributed variables were tested using the analysis of variance for repeated measures (RANOVA) model with effects for treatment, time, and treatment$\times$time interaction. The first measurement was used as a covariate in haemodynamic measurements. Time point-wise comparisons were done with the T-test. Cumulative doses of vasoactive medications were compared between groups using the Mann–Whitney U-test. Values are

presented as mean (SD). The analyses were carried out using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and operative data are presented in Table 1. No significant differences were detected between the treatment groups. The SI, CI, and HR measured by ICG_{WB} are presented in Figure 1. LCWI was higher in the LG compared with the CG ($P=0.003$, RANOVA) and there was no difference in systolic or mean arterial pressure between the groups during the study period. There was a trend towards lower values for SVRI in the LG compared with the CG during the postoperative period (P=NS). At baseline, transmitral flow velocity combined with annular velocity (E/E') was elevated in both groups. E/E' is presented in Figure 2A. Left atrial volume indexes were also suggestive for diastolic dysfunction (39.4 ml m^{-2} in the CG and 39.9 ml m^{-2} in the LG).

The LVEFs were normal in both groups at baseline. In the postoperative period, the LVEF decreased in the CG, but was maintained in the LG (Fig. 2B). On the fourth postoperative morning, the gradient measured across the aortic valve (peak/mean) was bigger in the LG compared with the CG: [33 (8)/17 (4) mm Hg] *vs* [24 (7)/12 (4) mm Hg], respectively, $P<0.05$ between groups. There was no difference in aortic valve size or in the valve type (a mechanical or biological) between the groups.

Levosimendan was rapidly absorbed and eliminated from plasma after study drug infusion ended. Twenty-four h after the start of infusion, the mean concentration was 30 (20) ng ml^{-1} and it was below the lower limit of quantification (i.e. <0.200 ng ml^{-1}) at 48 h. Both metabolites had a growing trend (Fig. 3) until 96 h after the start of the levosimendan infusion.

Fluid input was greater in the LG compared with the CG during drug infusion (from baseline to the morning of surgery) ($P=0.03$). From the morning of surgery to the first postoperative morning, there was no difference in total fluid balance 11 631 (3291) ml in the LG *vs* 9620 (2789) ml in the CG ($P=0.09$). The

Table 1 Patient characteristics and operative data. Results are expressed as mean (SD) or numbers. ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass

	Placebo (n = 12)	Levosimendan (n = 12)
Sex (male)	8	10
Age (yr)	75 (8)	76 (10)
Weight (kg)	77 (12)	84 (13)
Body surface area (m^2)	1.88 (0.20)	1.97 (0.18)
Preoperative β-blocker	7	11
Preoperative ACE inhibitor	4	6
Preoperative Ca-channel blocker	2	5
Preoperative statin	11	9
Preoperative LVEF (%)	69 (9)	63 (9)
Preoperative aortic valve gradient (mm Hg) peak	78 (12)	89 (22)
Mean	47 (8)	56 (17)
Operation time (min)	220 (48)	240 (40)
CPB time (min)	125 (29)	133 (21)

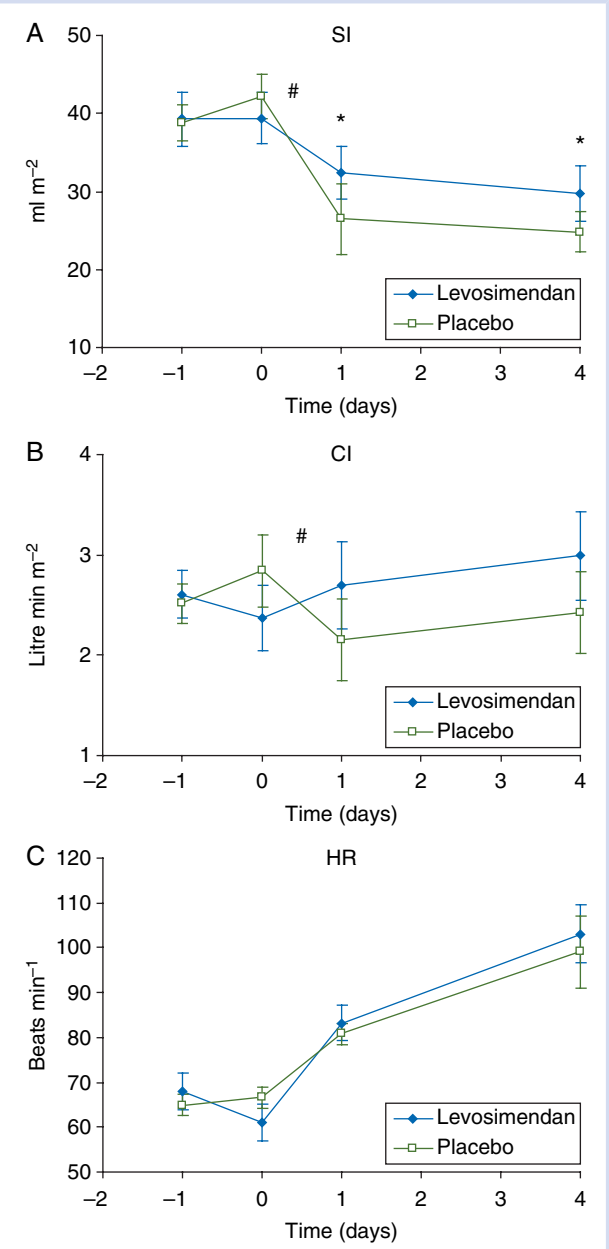

Fig 1 (A) SI, (B) CI, and (C) HR at baseline (−1), on the morning of surgery (0), and on the first (1) and fourth (4) postoperative mornings, measured by whole-body impedance cardiography. Results are expressed as mean (confidence intervals). *$P<0.05$ between the groups and # the significant difference between the groups from the first postoperative morning to the morning before surgery.

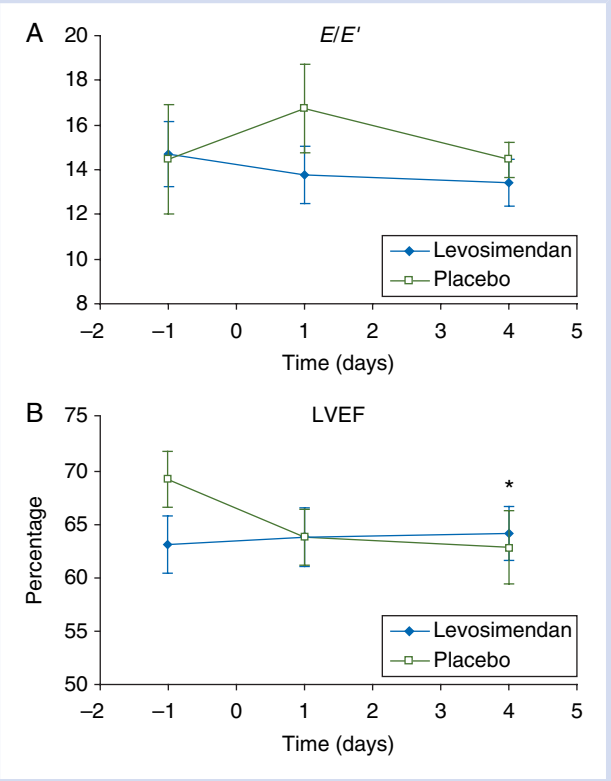

Fig 2 (A) *E*/*E*′ and (B) LVEF at baseline and on the first and fourth postoperative mornings. Results are expressed as mean (SEM). *$P<0.05$ for the change in LVEF between the groups from baseline to the fourth postoperative morning.

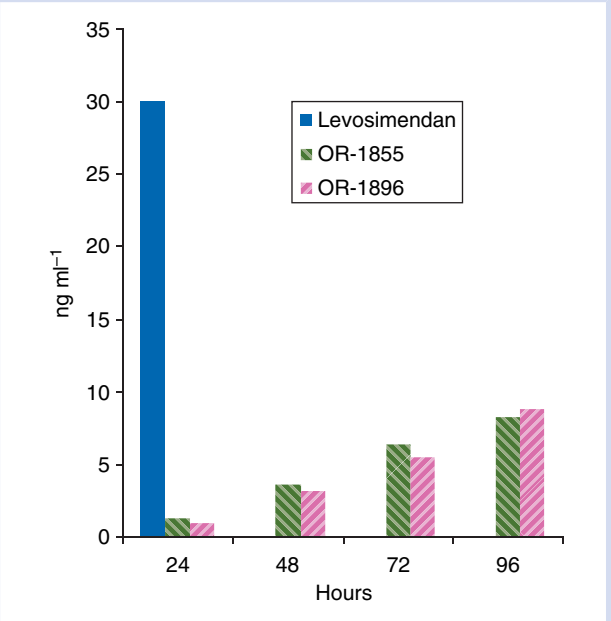

Fig 3 The concentration of levosimendan, OR-1855, and OR-1896 24, 48, 72, and 96 h after the start of levosimendan infusion. The operation started at 24 h.

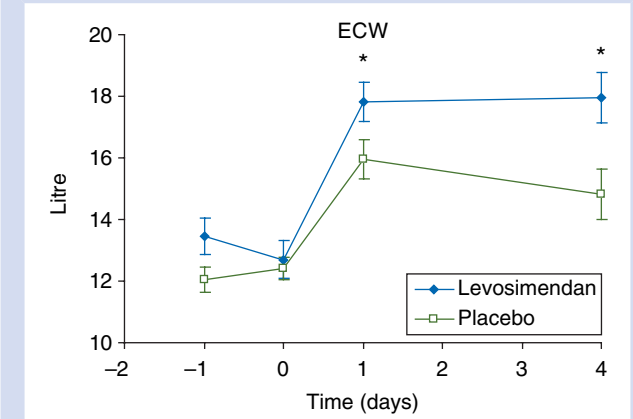

Fig 4 ECW at baseline (−1), on the morning of surgery (0), and on the first (1) and fourth (4) postoperative mornings. Results are expressed as mean (SEM). *$P<0.05$ between the groups.

fluid input (crystalloids, colloids, and blood products) and output was comparable between the groups. ECW was comparable between the groups before operation, but it was significantly higher in the LG, compared with the CG, during the postoperative period ($P= 0.008$ RANOVA; Fig. 4).

The LG required more norepinephrine during surgery and in the ICU compared with the CG [1.87 (1.23) *vs* 0.37 (0.57) mg, $P=0.001$ and 1.22 (0.99) *vs* 0.18 (0.30) mg, $P=0.001$, respectively]. Norepinephrine infusion was discontinued in all patients by the first postoperative morning. Otherwise, the need for vasoactive medication did not differ between the groups. At baseline, NT-proBNP was elevated in 10 patients in the LG compared with eight patients in the CG; 2088 (2541) *vs* 1232 (1010) ng litre^{-1}, $P=0.29$, respectively. After operation, NT-proBNP increased in both groups on the fourth postoperative morning; 3329 (2662) ng litre^{-1} in the LG *vs* 3298 (1933) ng litre^{-1} in the CG (P=NS). P-CK-MB and systemic lactate values were comparable between the groups throughout the study period. Myocardial injury was described using a strict criterion of P-CK-MB. In two patients in both groups, P-CK-MB exceeded 75 U litre^{-1} in the first postoperative morning. By the second postoperative morning, P-CK-MB was above 75 U litre^{-1} in one patient in the LG. The mechanical ventilation time did not differ between the groups: 586 (615) min in the LG *vs*. 340 (88) min in the CG ($P=0.20$). The length of stay in the ICU was 25.3 (9.7) h in the LG *vs* 25.6 (10.1) h in the CG and in the hospital 8.6 (3.3) days in the LG *vs* 8.8 (5.6) days in the CG (P=NS). One patient in the LG died on the first postoperative morning. The death was not related to study drug infusion.

Discussion

In this prospective randomized study, levosimendan improved haemodynamics during the 4 day postoperative period, when infused a day before surgery. The formation of metabolites was documented for this 4 day postoperative period.

Peak concentrations of the levosimendan metabolites have been observed at 2–4 days in heart failure patients,[16] whereas the concentration peaked at day 6 in cardiac surgery patients studied by Eriksson and colleagues.[17] In our study, the concentrations of metabolites showed an increasing trend until day 4. The concentrations on day 4 were higher than the peak concentration in the study by Eriksson and colleagues; the mean concentration of OR-1855 was 8.4 (3.3) ng ml^{-1} compared with the peak value of 6.6 (4.9) ng ml^{-1} reported by Eriksson and colleagues on day 6. Similarly, the mean concentration of OR-1896 was 8.8 (4.9) ng ml^{-1} compared with 7.7 (6.3) ng ml^{-1}. This supports our hypothesis that the formation of the metabolites is not disturbed by possible hypoperfusion caused by CPB, when levosimendan is started before operation. Eriksson and colleagues[17] also showed the concentration of levosimendan peaked ~2 h after infusion began. In our study, patients underwent surgery 24 h after starting the study drug infusion. The patients received the beneficial effects of levosimendan before operation and the metabolites were starting to increase early in the postoperative phase. The lowest concentration of OR-1896 that enhances haemodynamics is not available.

Levosimendan augments cardiac performance after cardiac surgery with CPB in patients with normal preoperative LV function.[8] In the present study, the LVEF was within the normal range in both groups at baseline. The LVEF decreased from the baseline value on the first and fourth postoperative days in the CG, but it remained constant in the levosimendan-treated patients. The effects of levosimendan, measured by ICG_{WB}, lasted throughout the study period. The SI remained significantly better in the LG compared with the CG and there was no difference in HR between the groups; therefore, the higher CI values in the LG were due to enhanced SI rather than tachycardia. Levosimendan was able to support cardiac function, which decreased in the CG despite the normal systolic function at baseline. The duration of the increase in cardiac output was 12–13 days in congestive heart failure patients.[16] This is consistent with our finding, although we do not know how long the difference remained in our study population. These observations suggest that levosimendan may prevent the myocardial dysfunction that often occurs after cardiac surgery.[18] The authors expected a decrease in the requirements of other inotropes; however, no differences were found in the requirements for inotropic support between the two study groups.

On the fourth postoperative morning, the gradient measured across the aortic valve was higher in the LG compared with the CG. The implanted valves were comparable in both groups. Higher values in the LG were likely due to the increased SI. Diastolic dysfunction was suggested by Doppler and tissue Doppler imaging. The diastolic function was assessed with E/E', which combines the influence of transmitral driving pressure and myocardial relaxation. De Luca and colleagues[19] have shown a decrease in LV filling pressure, assessed by E/E', after levosimendan treatment. In the present study, the difference between the groups was not significant despite a decreasing trend in the LG and an increasing trend in the CG. This may be due to the haemodynamic treatment protocol, which aimed at standardized filling pressures. The LG needed more fluids to achieve pre-set filling pressure. Statistically significant changes were not seen in any other measurements concerning diastolic function. The left atrial volume index, peak Doppler velocities of early (E) and late diastolic (A) flow, deceleration time of E-wave, and E/A ratio were not significantly different between treatment groups at any time point. Still, the SI increased, the LVEF remained constant, and diastolic function assessed with E/E' showed an increasing trend in the LG compared with the CG.

There was no significant difference in the NT-proBNP or P-CK-MB between the groups. This is in the NT-proBNP probably because, in our treatment protocol, fluids were infused to meet the PCWP goal; therefore, we were unable to see the decrease in filling pressures. A recent meta-analysis suggests that levosimendan is associated with a reduction in cardiac troponin release in cardiac surgery patients.[20] The release of the injury marker we used did not confirm this finding.

Tasouli and colleagues investigated starting the levosimendan infusion at different time points. In their study, patients were randomized to receive a continuous infusion of levosimendan (0.1 μg kg^{-1} min^{-1}) started either intraoperatively or after operation in the ICU. The earlier start was associated with a shorter ICU and hospital stay.[21] In our study, the length of the ICU or hospital stay did not differ between the groups, which may be due to small sample size.

ICG_{WB} is reportedly a reliable method of measuring cardiac output; comparisons with a bolus and continuous thermodilution and direct Fick methods showed that ICG_{WB} measures cardiac output accurately in different conditions (in the supine position, during head-up tilt, after induction of anaesthesia, and CABG).[14 22] Differences in cardiac output values between the ICG_{WB} and thermodilution methods were comparable with those between direct Fick and thermodilution methods. The repeatability of ICG_{WB} was nearly twice as good as that of thermodilution.[23 24] Therefore, ICG_{WB} is an adequate method to estimate cardiac output and its changes.

The exact volume of ECW in man is unknown. In invasive diagnostics, the distribution space of substances used for ECW volume estimation ranges from 15% (inulin and mannitol) to 23% (ions such as bromide and chloride) of body weight.[25] The ICG_{WB} device calculates ECW volume on the basis of the equation derived by Kolesnikov and colleagues,[26] which is fitted to thiosulphate space giving ECW values around 16% of body weight. The decrease in systemic vascular resistance caused by levosimendan resulted in changes in the fluid distribution from the central to peripheral vasculature. We do not believe this would significantly influence the measured R in the equation, and thereby increase the calculated ECW. The higher ECW values measured after

operation in the LG were probably due to the increased need for fluids in the preoperative phase.

Levosimendan may exert cardioprotective effects by the activation of K_{ATP} channels.[27 28] The authors made an effort to minimize confounding factors by selecting total i.v. anaesthesia. Volatile anaesthetics are known to affect K_{ATP} channel opening on reperfusion.[29] We also tried to minimize other confounding factors; two surgeons performed all the operations and one anaesthesiologist was responsible for the anaesthesia and CPB. The elective patients received the levosimendan bolus under continuous haemodynamic monitoring. In order to maintain adequate blood pressure, the patients in the LG needed volume loading. None of the patients needed norepinephrine. We suggest that in this patient group, the bolus is given with caution.

A limitation of this study is the small sample size. The sample size was calculated based on differences in stroke index. The study was not designed and powered to detect differences in other variables, for example, diastolic function or hospital stay. Another limitation in the present study is that the metabolites of levosimendan were only measured for 4 days and the peak concentrations were probably not seen. The cardiac surgery patients usually are transferred from our hospital to other hospitals on the fourth or fifth postoperative day; therefore, we were not able to take samples after the fourth day. The patients were invited to the hospital 3 h earlier than they normally would have been. If this can be done in the clinical practice, the preoperative infusion of levosimendan is not adding costs beyond the price of the drug.

In conclusion, the present study shows that CI and SI are enhanced for four postoperative days when levosimendan is infused before operation. The formation of levosimendan's metabolites also seems more efficient compared with perioperative dosing.

Acknowledgements

We thank Minna-Liisa Peltola and Pirjo Järventausta, research nurses, for their valuable technical assistance. Heini Huhtala, MS, was consulted for the statistical methods used.

Conflict of interest

H.L. and L.L. have lectured for Orion, the manufacturer.

Funding

This work was supported by grants from the Finnish Cultural Foundation, Competitive Research Funding of the Pirkanmaa Hospital District, Tampere University Hospital, Ida Montin Foundation, and Orion Pharma Ltd.

References

1 Mehta RH, Bruckman D, Das S, *et al.* Implications of increased left ventricular mass index on in-hospital outcomes in patients undergoing aortic valve surgery. *J Thorac Cardiovasc Surg* 2001; **122**: 919–28

2 Eagle KA, Guyton RA, Davidoff R, *et al.* ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004; **110**: e340–437

3 Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg* 2000; **90**: 1052–9

4 Haikala H, Kaivola J, Nissinen E, Wall P, Levijoki J, Linden IB. Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. *J Mol Cell Cardiol* 1995; **27**: 1859–66

5 Ukkonen H, Saraste M, Akkila J, *et al.* Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clin Pharmacol Ther* 2000; **68**: 522–31

6 Follath F, Cleland JG, Just H, *et al.* Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; **360**: 196–202

7 Tritapepe L, De Santis V, Vitale D, *et al.* Levosimendan pretreatment improves outcomes in patients undergoing coronary artery bypass graft surgery. *Br J Anaesth* 2009; **102**: 198–204

8 Nijhawan N, Nicolosi AC, Montgomery MW, Aggarwal 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

9 Morelli A, De Castro S, Teboul JL, *et al.* Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med* 2005; **31**: 638–44

10 Kivikko M, Antila S, Eha J, Lehtonen L, Pentikainen PJ. Pharmacokinetics of levosimendan and its metabolites during and after a 24-h continuous infusion in patients with severe heart failure. *Int J Clin Pharmacol Ther* 2002; **40**: 465–71

11 Erdei N, Papp Z, Pollesello P, Edes I, Bagi Z. The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. *Br J Pharmacol* 2006; **148**: 696–702

12 Banfor PN, Preusser LC, Campbell TJ, *et al.* Comparative effects of levosimendan, OR-1896, OR-1855, dobutamine, and milrinone on vascular resistance, indexes of cardiac function, and O_2 consumption in dogs. *Am J Physiol Heart Circ Physiol* 2008; **294**: H238–48

13 Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor-alpha concentrations in patients undergoing cardiopulmonary bypass. *Crit Care Med* 1993; **21**: 210–7

14 Koobi T, Kaukinen S, Turjanmaa VM, Uusitalo AJ. Whole-body impedance cardiography in the measurement of cardiac output. *Crit Care Med* 1997; **25**: 779–85

15 De Hert SG, Lorsomradee S, Cromheecke S, Van der Linden PJ. The effects of levosimendan in cardiac surgery patients with poor left ventricular function. *Anesth Analg* 2007; **104**: 766–73

16 Lilleberg J, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. *Eur J Heart Fail* 2007; **9**: 75–82

17 Eriksson HI, Jalonen JR, Heikkinen LO, *et al.* Levosimendan facilitates weaning from cardiopulmonary bypass in patients undergoing coronary artery bypass grafting with impaired left ventricular function. *Ann Thorac Surg* 2009; **87**: 448–54

18 Kloner RA, Przyklenk K, Kay GL. Clinical evidence for stunned myocardium after coronary artery bypass surgery. *J Card Surg* 1994; **9**: 397–402

19 De Luca L, Sardella G, Proietti P, *et al.* 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**: 172–7

20 Zangrillo A, Biondi-Zoccai G, Mizzi A, *et al.* Levosimendan reduces cardiac troponin release after cardiac surgery: a meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth* 2009; **23**: 474–478

21 Tasouli A, Papadopoulos K, Antoniou T, *et al.* Efficacy and safety of perioperative infusion of levosimendan in patients with compromised cardiac function undergoing open-heart surgery: importance of early use. *Eur J Cardiothorac Surg* 2007; **32**: 629–33

22 Kaukinen S, Koobi T, Bi Y, Turjanmaa VM. Cardiac output measurement after coronary artery bypass grafting using bolus thermodilution, continuous thermodilution, and whole-body impedance cardiography. *J Cardiothorac Vasc Anesth* 2003; **17**: 199–203

23 Koobi T, Kaukinen S, Turjanmaa VM. Cardiac output can be reliably measured noninvasively after coronary artery bypass grafting operation. *Crit Care Med* 1999; **27**: 2206–11

24 Koobi T, Kaukinen S, Ahola T, Turjanmaa VM. Non-invasive measurement of cardiac output: whole-body impedance cardiography in simultaneous comparison with thermodilution and direct oxygen Fick methods. *Intensive Care Med* 1997; **23**: 1132–7

25 Widdowson EM, Dickerson JWT. Chemical composition of the body. In: Comar CI, Bronner F, eds. *Mineral Metabolism: An Advanced Treatise*. *Vol II, The Elements, Part A*. New York: Academic Press, 1964; 12–3

26 Kolesnikov IS, Lytkin MI, Tishchenko MI, Shanin IN, Volkov IN. Total-body rheography in surgical diseases of the chest organs (in Russian). *Vestnik Khirurgii* 1981; **126**: 114–21

27 Kersten JR, Montgomery MW, Pagel PS, Warltier DC. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K(ATP) channels. *Anesth Analg* 2000; **90**: 5–11

28 Tritapepe L, De Santis V, Vitale D, *et al.* Preconditioning effects of levosimendan in coronary artery bypass grafting—a pilot study. *Br J Anaesth* 2006; **96**: 694–700

29 de Ruijter W, Musters RJ, Boer C, Stienen GJ, Simonides WS, de Lange JJ. The cardioprotective effect of sevoflurane depends on protein kinase C activation, opening of mitochondrial K(+)(ATP) channels, and the production of reactive oxygen species. *Anesth Analg* 2003; **97**: 1370–6