*Acta Anaesthesiol Scand 2008; **52**: 785–792*
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2008.01659.x

Effects of levosimendan on indocyanine green plasma disappearance rate and the gastric mucosal–arterial pCO_2 gradient in abdominal aortic aneurysm surgery

H. Leppikangas[1], J. J. Tenhunen[1], L. Lindgren[1], J.-P. Salenius[1] and E. Ruokonen[2]
[1]*Critical Care Medicine Research Group, Departments of Critical Care Medicine, Anesthesiology and Vascular Surgery, Tampere University Hospital, Tampere, Finland and* [2]*Department of Intensive Care, Kuopio University Hospital, Finland*

Background: Levosimendan has a dual mechanism of action: it improves myocardial contractility and causes vasodilatation without increasing myocardial oxygen demand. In a laboratory setting, it selectively increases gastric mucosal oxygenation in particular and splanchnic perfusion in general. The aim of our study was to describe the effects of levosimendan on systemic and splanchnic circulation during and after abdominal aortic surgery.
Methods: Twenty abdominal aortic aneurysm surgery patients were randomized to receive either levosimendan ($n = 10$) or placebo ($n = 10$) in a double-blinded manner. Both the mode of anaesthesia and the surgical procedures were performed according to the local guidelines. Automatic gas tonometry was used to measure the gastric mucosal partial pressure of carbon dioxide. Systemic indocyanine green clearance plasma disappearance rate (ICG-PDR) was used to estimate the total splanchnic blood flow.
Results: The immediate post-operative recovery was uneventful in the two groups with a comparable, overnight length of stay in the intensive care unit. Cumulative doses of additional vasoactive drugs were comparable between the groups, with a tendency towards a higher cumulative dose of noradrenaline in the levosimendan group. After aortic clamping, the cardiac index was higher [4(3.8–4.7) l/min/m^2 vs. 2.6(2.3–3.6) l/min/m^2; $P < 0.05$] and the gastric mucosal–arterial pCO_2 gradient was lower in levosimendan-treated patients [0.9(0.6–1.2) kPa vs. 1.7(1.2–2.1) kPa; ($P < 0.05$)]. However, the total splanchnic blood flow, estimated by ICG-PDR, was comparable [29(21–29)% vs. 20(19–25)%; NS]. Organ dysfunction scores (sequential organ dysfunction assessment) were similar between the groups on the fifth post-operative day.
Conclusion: Levosimendan favours gastric perfusion but appears not to have a major effect on total splanchnic perfusion in patients undergoing an elective aortic aneurysm operation.

Accepted for publication 31 January 2008

Key words: inotropy; calcium sensitizer; levosimendan; splanchnic perfusion; gastrointestinal tract; blood flow.

Gastrointestinal hypoperfusion may play an important role in the pathophysiology of overall tissue hypoperfusion abnormalities in major surgery, causing high mortality and increased cost of care (1). Impaired splanchnic perfusion may induce systemic inflammation and multiple-organ dysfunction (MOD). Perioperative bowel ischaemia and a significant increase in colonic epithelial apoptosis have been shown to occur as a response to open abdominal aortic surgery (2, 3). During abdominal aortic surgery, gut mucosal perfusion and colonic tissue flow decrease as measured by gastric tonometry and laser Doppler flowmetry (4). Previous attempts to find an ideal inodilator with preferential splanchnic vasodilatation have failed, and the effects of various vasoactive agents on total splanchnic, or selectively, on gastric perfusion are inconsistent (5, 6).

Levosimendan is a rather new calcium-sensitizing inodilator that enhances myocardial contractility (7) and produces both coronary and peripheral vasodilatation (8) without increasing the myocardial oxygen demand (9). Previously, levosimendan has been used in patients suffering from congestive heart failure (10), post-CABG and in septic shock (11). In an experimental setting in anaesthetized intact dogs, levosimendan appears to be superior to milrinone and dobutamine in increasing gastric mucosal oxygenation selectively without requiring major increases in systemic oxygen demand or

delivery (12). It favours splanchnic (total splanchnic, liver and renal) circulation under normal physiological conditions (13) and in experimental endotoxin shock (14–16). To date, the only limited clinical human data are available on the effects of levosimendan during major surgery, post-CABG surgery (17) or in septic shock in general or on regional perfusion (18). In post-CABG patients, levosimendan increased the cardiac output and stroke volume and decreased vascular resistance without increasing oxygen consumption (17). The clinical efficacy of levosimendan as an alternative to increasing the dose of dobutamine in septic shock has been shown by Morelli et al. (18).

We hypothesized that levosimendan could improve splanchnic blood flow and tissue perfusion perioperatively in major vascular surgery. To test our hypothesis, we measured the effect of levosimendan on splanchnic blood flow and tissue perfusion in patients undergoing elective aortic aneurysm surgery.

Methods

Patients

The Local Ethics Committee approved the study protocol. Patients with an infrarenal abdominal aortic aneurysm undergoing elective surgery were enrolled after written, informed consent. We excluded patients with aortic valvular and occlusive disease or known sensitivity for an adverse reaction to levosimendan. We randomized the patients into a placebo ($n = 10$) or a levosimendan ($n = 10$) group. Randomization (sealed opaque envelopes) was performed by the pharmacist of the satellite pharmacy at the department of intensive care unit (ICU). The pharmacist also prepared and diluted the study drugs thereby ensuring that the investigators, surgeons, anaesthesiologists, research assistants and medical and nursing staff in the ICU and on the ward were blinded to the group assignment.

Mode of anaesthesia, fluid therapy and use of vasoactive drugs

A radial arterial cannula and a pulmonary artery catheter (Arrow®, Reading, PA, USA) were inserted under local anaesthesia before the operation to enable continuous haemodynamic monitoring. An epidural catheter (Portex®, Watford, UK) was inserted at the thoracolumbal T12–L1 intervertebral space using a standard loss of resistance technique under local anaesthesia for post-operative pain relief, after which the baseline measurements were made. The patients in the treatment group received a levosimendan (Simdax®, Orion Pharma, Finland) 24 μg/kg i.v. bolus over 30 min before induction of anaesthesia. The control patients received a placebo (thiamin-coloured 5% glucose) infusion of equivalent volume over the same time interval. The levosimendan infusion 0.2 μg/kg min or placebo infusion was continued for 24 h.

The anaesthesia was induced with propofol (1.5–2.5 mg/kg according to clinical needs), fentanyl (2–3 μg/kg) and cisatracure (0.15 mg/kg). After tracheal intubation, the lungs were mechanically ventilated with an oxygen–air mixture (FiO_2 0.40–0.60 to maintain peripheral SpO_2 over 92%). Anaesthesia was maintained with an infusion of propofol adjusted to maintain state entropy (SE) levels between 40 and 60, the target being 50 (Entropy Sensor®, GE Healthcare, Milwaukee, WI, USA) and fentanyl (1–2 μg/kg bolus) combined. Neuromuscular blockade was achieved with bolus injections of cisatracurium according to clinical needs. It was monitored with ulnar nerve train of four (TOF) stimulation and neuromuscular transmission monitoring (TOF-Watch®, Organon, the Netherlands). The tidal volumes were adjusted in the operating theatre and post-operative unit according to the ARDS network guidelines of 6–8 ml/kg of ideal body weight (19). The use of dobutamine was aimed to maintain the cardiac index $>2.0\,l/min/m^2$. Mean arterial pressure (MAP) was maintained >65 mmHg using norepinephrine. Before any use of inotropes or vasoconstrictors, the intravascular volume was ensured by adjusting pulmonary artery occlusion pressure (PAOP) to 8–12 mmHg. Mixed venous oxygen saturation was maintained >70% by infusing crystalloids, colloids and packed red blood cells to maintain the haemoglobin concentration over 80 g/dl.

Surgical procedure

The surgical procedure was standardized. The same individual senior surgeons were chosen to minimize the confounding effect of differences in the surgical technique and skills. The abdominal aorta was exposed through a full midline laparotomy. An infrarenal clamp was accomplished under systemic heparinization (dose 5000 IU). The aortic occlusion time was recorded. A dacron Y-prosthesis was used to reconstruct the aortic and iliac arteries. After the anastomoses were prepared, the lower trunk blood circulation was

returned, careful haomoestasis was ensured and the laparotomy was closed in layers.

Haemodynamic monitoring

The heart rate, MAP, central venous pressure (CVP), PAOP and cardiac output were recorded. (HP, Palo Alto, CA, USA until 9/2005 then Philips, Amsterdam, the Netherlands). The derived cardiovascular variables (cardiac index and systemic vascular resistance) were calculated using standard formulae. Cardiac output was measured by bolus injectates in triplicate using 10 ml of room-temperature 0.9% sodium chloride. Haemodynamic data were collected at the following time points: at baseline, 30 min after induction of anaesthesia, before aortic clamping, 60 min after clamp, on admission to the ICU, 4 h post-ICU admission and 24 h after levosimendan/placebo bolus. Standard 12-lead ECG recordings were obtained perioperatively before surgery, immediately post-operatively and after 20–24 h on the first post-operative day.

Post-operative pain treatment

The epidural infusion (bupivacain 0.25%+Nacl 0.9% 26 ml+fentanyl 200 μg 2–7 ml/h) with per oral paracetamol was started at arrival on ICU.

Tonometry and indocyanine green plasma disappearance rate

To assess a surrogate for gastric mucosal perfusion, mucosal pCO_2 was measured and gastric mucosal to arterial pCO_2 gradient was calculated during the perioperative period by a gastric tonometer (Tonocap®, Datex, Ohmeda, Finland). The tonometer catheter was inserted after the induction of anaesthesia, and the correct placement in the stomach was confirmed manually in the beginning of surgery and by chest X-ray obtained in the ICU. Total splanchnic blood flow was estimated by measuring the indocyanine green plasma disappearance rate (ICG-PDR) transcutaneously (20, 21). Briefly, each patient was connected to an ICG finger clip, which was connected to a liver function monitor (LiMon®, Pulsion Medical Systems, Germany). A Dose of ICG 0.25 mg/kg (22) was injected through a central venous line of the pulmonary artery catheter at baseline, before and during aortic clamping and post-operatively. Arterial, central venous and mixed venous blood–gas tensions and oxygen saturations, haemoglobin and lactate concentrations were measured before induction of anaesthesia, before and during aortic occlusion and at the end of surgery. Troponine T concentrations were measured at admission to the ICU and at the first post-operative morning.

Primary end point parameters

The primary endpoint parameters were cardiac index and stroke volume index. Surrogates for total splanchnic perfusion and gastric wall perfusion were ICG-PDR and gastric mucosal–arterial pCO_2 gradient. Mortality, length of ICU stay and morbidity were considered to be secondary endpoints.

Data analysis and statistics

ICG-PDR was a rather new method and this is why we did not have enough data for sample size calculations. Instead, we used splanchnic blood flow and mucosal pH as surrogates. We assumed an SD of 0.2 l/min/m^2 for splanchnic blood flow and 0.068 for mucosal pH and a within-subject coefficient of variation of 4% for splanchnic blood flow measurements (23, 24). Using a two-sided α of 0.05, this would allow us to detect a change of 0.18 litre/min/m^2 in splanchnic blood flow and 0.06 pH units in mucosal pH with 80% power with 10 evaluable patients per group. One patient was excluded from post-operative analyses but was included for perioperative data. The group allocation was unblinded for this patient (placebo) because of profound post-operative oozing. Another patient was randomized to supplement the sample size.

The majority of the data was normally distributed as tested by the Kolmorogov–Smirnov test. Based on the kurtosis and skewness of the data, non-parametric statistical tests were used. Data are therefore presented as median (25–75th percentiles). We used Friedman two-way analysis of variance. When the Friedman test was found to be significant, the Wilcoxon signed-rank test was used to compare the values at baseline vs. each time point. Two-tailed tests were used and the Bonferroni correction was not applied. Comparably, when significant, post-Friedman analysis between the groups was performed by the Mann–Whitney *U*-test. The χ^2-test was used to compare the need for additional vasoactive drugs in the two groups. SPSS software (SPSS™ 15.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A *P*-value of <0.05 was considered to be significant.

Results

The patient characteristics were comparable in the two groups (Table 1). Six patients in the placebo

Table 1

Patient characteristics in levosimendan ($n = 10$) and placebo-treated groups ($n = 11$ at the baseline).

	Placebo	Levosimendan
Age (years)	72 (61; 74)	64 (60; 72)
Sex (M/F)	10/1	6/4
Weight (kg)	75 (65; 78)	80 (69; 94)
DM	0	2
HTA	7	7
COPD	3	1
CAD	2	1
β-blockers	6	4
SOFA post-operative day 1	3 (2.25; 4)	3.5 (3; 4.75)
SOFA post-operative day 5	1 (0.5; 1)	0 (0; 0)
Duration of surgery (min)	213 (191; 254)	223 (183; 235)
Blood loss (ml)	2175 (1200; 3075)	1300 (1050; 2000)

DM, diabetes mellitus; HTA, hypertonia; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; SOFA, sequential organ dysfunction assessment.

group and four patients in the levosimendan group used β blockers before surgery. One patient in the levosimendan group required intensive care for 6 days because of post-operative bleeding, two reoperations for haemostasis and development of non-dialysis-dependent acute renal failure. One patient in the placebo group and one in the levosimendan group required intensive care for 2 days because of oliguria and respiratory failure, respectively. Otherwise, the post-operative recovery was uneventful in both groups with an overnight post-operative period in ICU. One patient was excluded from further statistical analysis after the code was opened because of clinical judgement necessary for profound post-operative bleeding.

The peri- and post-operative haemodynamic characteristics are shown in Table 2. At baseline, before surgery, there were no differences between the levosimendan and the control groups in haemodynamic variables or splanchnic blood flow. During surgery until 60 min after aortic clamping, the cardiac index was higher in levosimendan-treated patients (Fig. 1a). Levosimendan was associated with a stable heart rate while in the placebo group the heart rate decreased from baseline to 60 min after aortic clamping. Stroke volume remained comparable in the two groups (Table 2, Fig. 1b). The gastric mucosal to arterial pCO_2 gradient was lower in the levosimendan group after 60 min of aortic clamping [0.9 (0.6–1.2) kPa vs. 1.7 (1.1–2.1) kPa; $P = 0.003$] (Fig. 2a). Concomitantly, ICG-PDR [29 (21–29)% vs. 20 (19–25)%; $P = 0.055$] was comparable between the groups throughout the study period (Fig. 2b). There was no difference in gastric pH_i between groups.

Six patients in the levosimendan group and three patients in the placebo group received norepinephrine during the operation ($P < 0.05$). Post-operatively, four patients in the levosimendan group, but none in the placebo group received norepinephrine ($P < 0.05$). Cumulative doses of norepinephrine were 1.5 μg/kg (0; 6.3) and 0 μg/kg (0; 0.9) in the levosimendan and the placebo groups, respectively ($P = 0.12$). Dobutamine was needed for two patients in the placebo group perioperatively and for one patient in both groups post-operatively to maintain sufficient cardiac performance. Two patients in the levosimendan group and four patients in the control group received sodium nitroprusside to control systemic blood pressure in the operating theatre, and one patient in both groups post-operatively. Neither ST-segment changes nor troponin T release were detected in either group post-operatively. One patient receiving levosimendan died during hospitalization because of acute exacerbation of severe COPD.

Discussion

The main findings of our study were: firstly, levosimendan increased cardiac output while stroke volume remained unchanged. Secondly, the patients receiving levosimendan needed norepinephrine more often for systemic hypotension. Thirdly, contrary to our hypothesis, levosimendan increased systemic blood flow but the total splanchnic blood flow did not increase as estimated by the PDR of indocyanine green dye (PDR %/min). Fourthly, even though the total splanchnic blood flow did not increase, the gastric mucosal to arterial pCO_2 gradient remained lower in the levosimendan group, suggesting higher gastric mucosal perfusion.

A previous report by Morelli et al. (18) shows that levosimendan increased gastric mucosal perfusion in patients with septic myocardial depression, decreased the pCO_2 gradient and increased capillary blood flow measured by laser Doppler flow. A decreased pCO_2 gradient was similarly seen in our study and by Morelli et al., who also demonstrated increased gastric capillary blood flow. This may show that also in our study gastric mucosal perfusion increased rather than e.g., the Haldane effect (25). Regional perfusion heterogeneity has been described previously by several

Table 2

Haemodynamic characteristics in levosimendan ($n = 10$) and placebo-treated groups ($n = 11$ from the baseline until clamp60, $n = 10$ thereafter).

	Baseline	Pre-clamp	Clamp 60	ICU 4 h	Pop 1	*P*-value, Friedman
HR (beats/min)						
Levosimendan	70 (64, 74)	74 (65, 81)†	73 (66, 77)†	83 (69, 95)	90 (86, 102)*,†	0.003
Placebo	60 (59, 62)	53 (51, 59)*	53 (47, 59)*	65 (55, 76)	78 (72, 82)*	0.000001
MAP (mmHg)						
Levosimendan	95 (83, 107)	82 (70, 84)*,†	74 (68, 78)*	70 (63, 76)*	70 (66, 78)*	0.00002
Placebo	99 (88, 105)	91 (87, 98)	78 (71, 85)*	82 (66, 88)*	79 (69,93)*	0.000001
CVP (mmHg)						
Levosimendan	7 (5, 8)	9 (7, 10)	9 (8, 10)	7 (4, 8)	4 (1, 8)	0.00007
Placebo	6 (3, 8)	9 (6, 13)*	9 (7, 14)*	5 (4, 6)	3 (1, 4)	0.000003
PAOP (mmHg)						
Levosimendan	10 (7, 11)	12 (10, 14)	12 (11, 13)	9 (7, 13)	7 (6, 11)	0.001
Placebo	11 (6, 12)	13 (10, 17)	11 (9, 16)	9 (5, 11)	9 (5, 10)	0.053
SVRI (dyne/s cm^5 m^2)						
levosimendan	2160 (1960, 2502)	1252 (1052, 1772)*,†	1284 (1052, 1313)*,†	1398 (1137, 2005)*	1356 (1137, 1562)*,†	0.009
Placebo	2153 (1788, 2364)	2302 (2125, 2529)	2231 (1444, 2744)	2049 (1688, 2213)	1730 (1650, 1956)*	0.027
SvO_2 (%)						
Levosimendan	73 (71, 76)	77 (73, 80)	71 (68, 76)	67 (64, 71)*	65 (57, 71)*	0.0003
Placebo	75 (71, 80)	76 (71, 80)	72 (68, 76)	65 (59, 72)*	70 (66, 75)	0.003
Hb (g/l)						
Levosimendan	121 (118, 129)	101 (89, 104)*	76 (67, 80)*	87 (80, 98)*	95 (88, 99)*	$<10^{-6}$
Placebo	121 (118, 124)	102 (92, 102)*	62 (59, 71)*	84 (73, 96)*	95 (86, 96)*	$<10^{-6}$
Arterial lactate (mmol/l)						
Levosimendan	0.6 (0.5; 1.1)	0.8 (0.5; 1.3)	1.0 (0.6; 1.9)*	1.3 (1.0; 1.9)*	0.7 (0.5; 1.0)	0.001
Placebo	0.7 (0.5; 0.8)	0.6 (0.6; 0.7)	0.6 (0.6; 0.8)	1.2 (1.0; 1.8)*	0.6 (0.5; 1.0)	$<10^{-6}$
PVRI (dyne/s cm^5 m^2)						
Levosimendan	213 (129, 230)	152 (114, 218)	228 (155, 303)	203 (194, 260)	199 (141, 302)	0.48
Placebo	193 (114, 251)	174 (101, 229)	131 (66, 198)	205 (142, 236)	210 (91, 293)	0.86
Ph_i						
Levosimendan	7.38 (7.34; 7.44)‡	7.30 (7.27; 7.34)	7.28 (7.27; 7.33)	7.27 (7.23; 7.28)	7.31 (7.26; 7.35)	0.002
Placebo	7.40 (7.34; 7.40)‡	7.27 (7.24; 7.32)	7.28 (7.21; 7.32)	7.26 (7.23; 7.28)	7.33 (7.30; 7.36)	0.001
Temperature (°C)						
Levosimendan	36.4 (36.1; 36.5)	35.6 (35.1; 35.8)*	35.8 (35.2; 35.9)*	36.9 (36.1; 37.1)	37.5 (36.7; 37.7)*	$<10^{-6}$
Placebo	36.2 (36.1; 36.2)	35.3 (35.2; 35.8)*	35.2 (35.1; 35.8)*	36.9 (36.5; 37.2)	37.8 (37.5; 37.9)*	$<10^{-6}$

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; SVRI, systemic vascular resistance index; SvO_2, mixed venous oxygen saturation; Hb, hemoglobin; PVRI, pulmonary vascular resistance index.

*$P < 0.05$ by Wilcoxon's signed-rank test (against the baseline) and

†$P < 0.05$ by Mann–Whitney *U*-test (between the groups).

‡ 30 min after induction of anaesthesia.

authors in an experimental (26, 27) or a clinical setting (5). Gastric mucosal perfusion changes do not reflect changes in other parts of the GI tract (27) or in the splanchnic region overall. In our study, ICG-PDR did not increase even with an increased cardiac index. This could imply that splanchnic blood flow did not increase in parallel with increasing cardiac index. However, the literature supporting the idea that ICG-PDR is a reliable surrogate for total splanchnic blood flow is limited. A fair conclusion might be that levosimendan was not associated with an enhanced hepatic blood flow/metabolism under this clinical condition. Concomitantly, with increasing cardiac index, we observed a lower gastric mucosal to arterial pCO_2 gradient in the levosimendan-treated patients. This may imply that indeed, levosimendan attenuates or limits gastric mucosal perfusion deficit during aortic cross-clamping. Morelli et al. (18) found that levosimendan improved systemic and regional perfusion in patients with a septic cardiac dysfunction under conditions where 5 μg/kg/min of dobutamine was no longer efficacious. Levosimendan increased gastric mucosal flow (reduction in $P_{g-a}CO_2$), creatinine clearance and urinary output while it decreased lactate concentrations. They did not measure or estimate the total splanchnic blood flow.

Cardiac output was increased in response to levosimendan even though the heart rate remained unchanged. Therefore, there could be an increase in stroke volume, even though a statistical difference was not detected probably due to the small number of patients. The stability in heart rate in the levosimendan group is also noteworthy compared with the trend towards lower heart rates in placebo

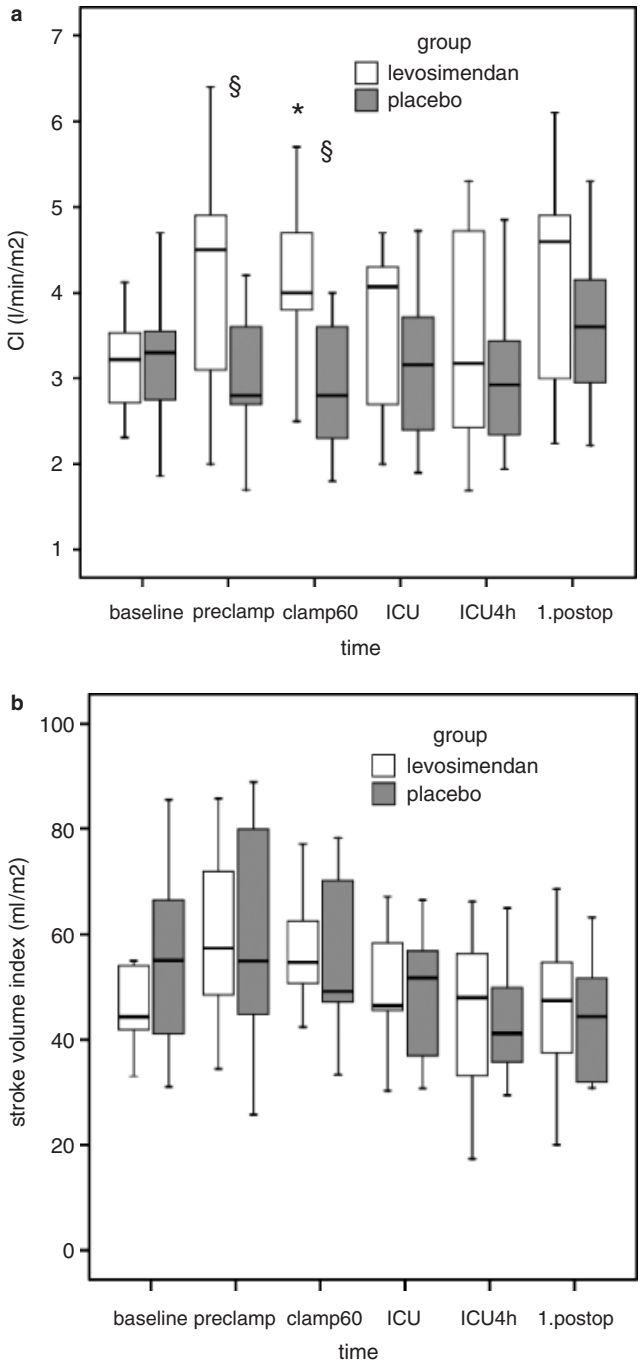

*Fig. 1. Cardiac index (a) and stroke volume index (b) in levosimendan-(white columns) and placebo-treated patients (black columns) at baseline, before aortic clamping (pre-clamp), 60 min after aortic clamping (clamp60), at admission to the intensive care unit (ICU), 4 h after admission (ICU4h) and in the first post-operative morning (1. postop). *P < 0.05 by Wilcoxon's signed-rank test (against the baseline) and §P < 0.05 by Mann–Whitney U-test (between the groups).*

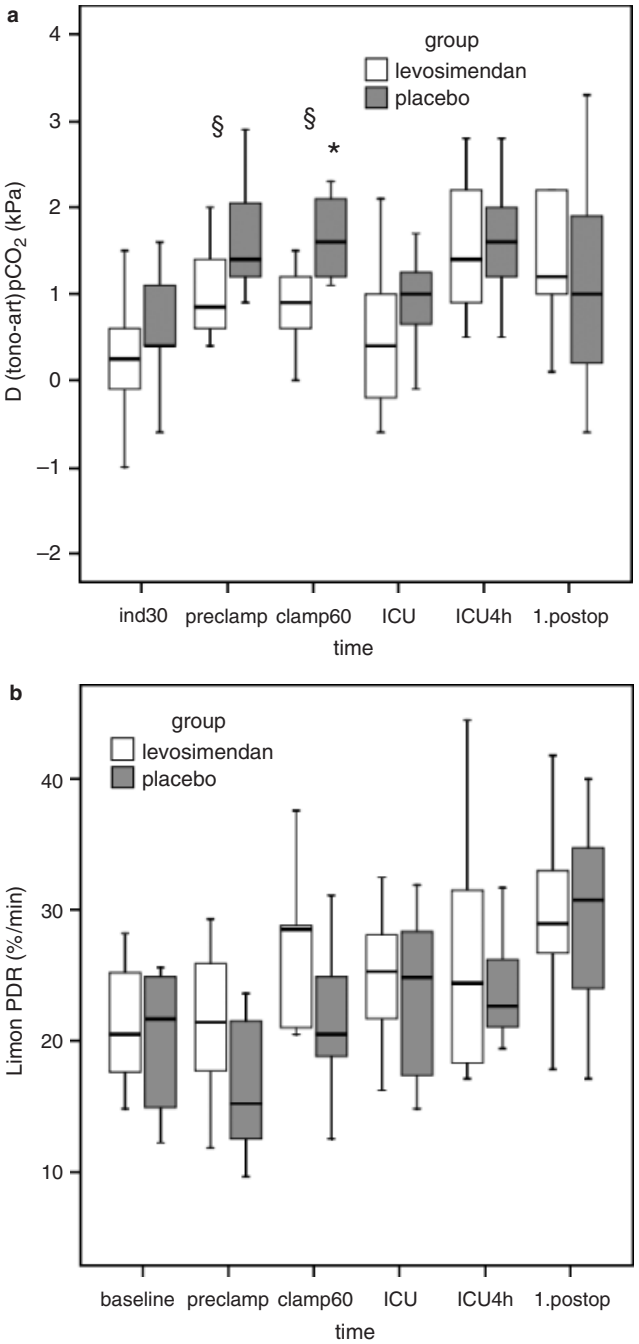

*Fig. 2. Gastric mucosal to arterial pCO2 gradient (a) and indocyanine green disappearance rate (ICG-PDR)(b) in levosimendan (white columns) and placebo-treated groups (black columns) patients at the baseline or 30 min after the induction of anaesthesia (ind30) and before aortic clamping (pre-clamp), 60 min after aortic clamping (clamp60), at admission to intensive care unit (ICU), 4 h after admission (ICU4h) and in the first post-operative morning (1. postop). *P < 0.05 by Wilcoxon's signed-rank test (against the baseline) and §P < 0.05 by Mann–Whitney U-test (between the groups).*

group in the beginning of surgery (Table 2). In the previous literature, levosimendan was associated with improved cardiac performance without increasing myocardial oxygen consumption (9). Even though we did not measure myocardial oxygen consumption, it is reasonable to speculate that stable heart rates may be associated with a higher myocardial oxygen consumption compared with our control patients. Previously, levosimendan was not associated with increased heart rate during septic shock-related myocardial depression (18). In our study, no troponin T release occurred in either of the groups. ST-segment changes were not detected during the study period. These findings may indicate that no myocardial ischaemia occurred and somewhat higher heart rates were well tolerated by our levosimendan-treated patients.

There are limitations in our present clinical study: Firstly, the number of patients included was small and the limited data available with PDR method do not make it possible to calculate the sample size reliably. However, we used previoius data from studies on splanchnic circulation in similar clinical settings, which may have resulted in too a small sample size. The use for other vasoactive drugs was an additional confounding factor: the need for norepinephrine was different between the groups, and therefore interaction between levosimendan and norepinephrine in terms of mucosal perfusion is possible. From the clinical perspective, this is an important finding. The need of other vasoactive drugs may increase in association with the use of levosimendan. Thereby, the overall effects on different vascular beds may be unpredictable. It might be on overstatement to simply suggest that the results presented herein could only be related to levosimendan. Secondly, we could not estimate the total splanchnic blood flow directly (hepatic vein catheter). Rather we used the peripheral detection of ICG clearance. After injection into circulation, ICG is nearly completely eliminated unchanged by the liver into bile without enterohepatic recirculation (28). The ICG-PDR has been found to be a good predictor of survival in critically ill patients (29, 30). At best, it reflects the total splanchnic blood flow without separating hepatic arterial from portal flow (31). We did not measure gastric mucosal capillary perfusion (laser Doppler flow). Rather, we used a surrogate for the gastric perfusion. To some degree, we can state the gastric mucosal–arterial pCO_2 gradient reflects the adequacy of total splanchnic perfusion.

In conclusion, levosimendan, a new inodilator, increases the cardiac index, and seems not to favour total the splanchnic blood flow but may direct blood flow preferentially towards the gastric wall in abdominal aortic surgery.

References

1. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is assosiated with increased post-operative complications and cost. *Intensive Care Med* 1994; **20**: 99–1042.
2. Syk I, Brunkwall J, Ivancev K et al. Postoperative fever, bowel ischemia and cytokine response to abdominal aortic aneurysm repair – a comparison between endovascular and open surgery. *Eur J Vasc Endovasc Surg* 1998; **15**: 398–405.
3. Ghosh J, Khwaja N, Howarth V et al. Colonic epithelial apoptosis during conventional and endoluminal aortic surgery. *Br J Surg* 2005; **92**: 443–8.
4. Nakatsuka M. Assessment of gut mucosal perfusion and colonic tissue blood flow during abdominal aortic surgery with gastric tonometry and laser doppler flowmetry. *Vasc Endovasc Surg* 2002; **36**: 193–8.
5. Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *Br J Anaesth* 1995; **74**: 149–54.
6. Tenhunen JJ, Martikainen TJ, Uusaro A et al. Dopexamine reverses colonic but not gastric mucosal perfusion defects in lethal endotoxin shock. *Br J Anaesth* 2003; **91**: 878–85.
7. Guarracino F, Cariello C, Danella A et al. Effect of levosimendan on ventriculo-arterial coupling in patients with ischemic cardiomyopathy. *Acta Anaesthesiol Scand* 2007; **51**: 1217–24.
8. Haikala H, Kaivola J, Nissinen E et al. Cardiac troponin C as a target protein for a novel calsium sensitizing drug, levosimendan. *J Mol Cell Cardiol* 1995; **27**: 1859–66.
9. Ukkonen H, Saraste M, Akkila J et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clin Pharmacol Ther* 2000; **68**: 522–31.
10. 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.
11. Mebazaa A. The SURVival of Patients with Acute Heart Failure in Need if IntraVEnous Inotropic Support (SURVIVE) trial. Late-breaking Clinical Trials, 13–16 November 2005. American Heart Association, Annual Scientific Session. Dallas, TX.
12. Schwarte LA, Picker O, Bornstein SR et al. Levosimendan is superior to milrinone and dobutamine in selectively increasing mircrovascular gastric mucosal oxygenation in dogs. *Crit Care Med* 2005; **33**: 135–42.
13. Pagel PS, Hettrick DA, Warltier DC. Influence of levosimendan, pimobendan, and milrinone on the regional distribution of cardiac output in anaesthetized dogs. *Br J Pharmacol* 1996; **119**: 609–15.
14. Zager RA, Johnson AC, Lund S et al. Levosimendan protects against experimental endotoxemic acute renal failure. *Am J Physiol Renal Physiol* 2006; **290**: F1453–6.
15. Oldner A, Konrad D, Weitzberg E et al. Effects of levosimendan, a novel inotropic calsium-sensitizing drug, in experimental septic shock. *Crit Care Med* 2001; **29**: 2185–93.

16. Dubin A, Murias G, Sottile JP et al. Effects of levosimendan and dobutamine in experimental acute endotoxemia: a preliminary controlled study. *Intensive Care Med* 2007; **33**: 485–94.
17. Lilleberg J, Nieminen MS, Akkila J et al. Effects of a new calcium sensitizer, levosimendan, on hemodynamics, coronary blood flow and myocardial substrate utilization early after coronary bypass grafting. *Eur Heart J* 1998; **19**: 660–8.
18. Morelli A, De Castro S, Teboul J-L et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med* 2005; **31**: 638–44.
19. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **2**: 1301–8.
20. Kuntz HD, Schregel W. Indocyanine green: evaluation of liver function – application in intensive care medicine. In: Lewis FR, Pfeiffer UJ, eds. *Fiberoptics in critical care monitoring*. Berlin Heidelberg NY: Springer, 1990: 57–62.
21. Sakka S, Reinhart K, Meier-Hellmann A. Comparison of invasive and non-invasive measurements of indosyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable heamodynamics. *Intensive Care Med* 2001; **26**: 1553–6.
22. Sakka S, Koeck H, Meier-Hellmann A. Measurement of indocyanine green plasma disappearance rate by two different dosages. *Intensive Care Med* 2004; **30**: 506–9.
23. Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by Fick principle in man and problems in the use of indocyanine green. *Cardiovasc Res* 1995; **30**: 106–12.
24. Parviainen I, Väisänen O, Ruokonen E et al. Effect of nasogastric suction and ranitidine on the calculated gastric mucosal pH. *Intensive Care Med* 1996; **22**: 319–23.
25. Jakob SM, Kosonen P, Ruokonen E et al. The Haldane effect – an alternative explanation for increasing gastric mucosal pCO_2 gradients? *Br J Anaesth* 1999; **83**: 740–6.
26. Hiltebrand LB, Krejci V, Banic A et al. Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock. *Critical Care Med* 2000; **28**: 3233–41.
27. Tenhunen JJ, Uusaro A, Karja V et al. Apparent heterogeneity of regional blood flow and metabolic changes within splanchnic tissues during experimental endotoxin shock. *Anesth Analg* 2003; **97**: 555–63.
28. Wiengand BD, Ketterer SG, Rapaport E. The use of indocyanine green for the evaluation of hepatic function and blood flow in man. *Am J Dig Dis* 1960; **5**: 427–36.
29. Kholoussy AM, Pollack D, Matsumoto T. Prognostic significance of indocyanine green clearance in critically ill surgical patients. *Crit Care Med* 1984; **12**: 115–6.
30. Sakka SG, Reinhart K, Meier-Hellmann A. Prognostic value of the indocyanine green plasma disappearance rate in critically ill patients. *Chest* 2002; **122**: 1715–20.
31. Stehr A, Ploner F, Traeger K et al. Plasma disappearance of indocuanine green: a marker for excretory liver function? *Intensive Care Med* 2005; **31**: 1719–22.

Address:
Heli Leppikangas
Department of Intensive Care
Tampere University Hospital
PO Box 2000
33521 Tampere
Finland
e-mail: heli.leppikangas@pshp.fi