Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting

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Aims The aim of the study was to evaluate the effects on systemic and coronary haemodynamics and myocardial substrate utilization of a new calcium sensitizer, levosimendan, after coronary artery bypass grafting.

Methods and Results Twenty-three low-risk patients were included in this randomized and double-blind study. They received placebo (n=8), 8 (n=8) or 24 (n=7) µg·kg⁻¹ of levosimendan after coronary artery bypass operation. Systemic and coronary sinus haemodynamics with thermodilution and myocardial substrate utilization were measured. The heart rate increased 11 beats·min⁻¹ after the higher dose (P<0·05). Cardiac output increased by 0·7 and 1·6l·min⁻¹ (P<0·05 for both) after 8 and 24 µg·kg⁻¹ of levosimendan, respectively. Systemic and pulmonary vascular resistance decreased significantly after both doses. Coronary sinus blood flow increased by 28 and 42 ml/(P=0·054 for the combined effect) after the lower and higher dose, respectively. Myocardial oxygen consumption or substrate extractions did not change statistically significantly.

Conclusion Despite improved cardiac performance, levosimendan did not increase myocardial oxygen consumption or change myocardial substrate utilization. Thus levosimendan has the potential to treat low cardiac output states after cardiopulmonary bypass surgery.

Key Words: Coronary haemodynamics, cardiac surgery, calcium sensitizers, cardiac metabolism, levosimendan.

Introduction

Despite cardioplegic protection, surgically induced global ischaemia and reperfusion of previously hypoperfused areas of myocardium lead to a variable degree of stunning and frequently require inotropic support to reverse depressed contractility. Most currently available inotropic drugs enhance myocardial contractility by increasing concentrations of intracellular calcium, which leads to an increase in myocardial oxygen consumption[1]. Substrate utilization also has profound effects on myocardial oxygen consumption. A complex interaction exists between fatty acid and glucose utilization. Since a shift from glucose/lactate to fatty acids in substrate utilization is a major determinant of the oxygen consumption of the heart, it is important to understand how inotropic intervention affects substrate utilization[2–4].

Levosimendan, the active (-)-enantiomer of simendan, is a new calcium sensitizer that acts by binding calcium dependently to cardiac troponin C, without any effect on myofibrillar ATPase[5]. It has been shown to shift the Ca²⁺ tension curve to the left in chemically skinned fibres of guinea pig papillary muscle. It has been proposed that levosimendan stabilizes the Ca²⁺-induced conformational change of troponin C. Its effect is maximal when intracellular calcium concentration is high during early systole and minimal during relaxation when calcium concentration is low. The detrimental effects of calcium sensitization on ventricular relaxation may thus be avoided by this calcium-dependent action. It has also been demonstrated that levosimendan does not impair relaxation of intact paced guinea pig papillary muscles or of isolated failing human
myocardium. In addition, levosimendan has selective phosphodiesterase III inhibitory properties, but no increase of cyclic adenosine monophosphate at therapeutic concentrations contributes to the inotropic effect of levosimendan.

Végh et al. have shown in anaesthetized dogs after experimental acute heart failure induced by ligation of the left anterior descending artery and critical constriction of the left circumflex artery that levosimendan increased coronary blood flow and myocardial contractility depressed by ischaemia. We have previously demonstrated that levosimendan has combined inotropic and systemic vasodilatory effects in both healthy volunteers and patients with left ventricular dysfunction. It seems that levosimendan is a potent dilator of both arteriolar and venous beds. In patients with normal filling pressures, a decrease in preload probably prevents increases in cardiac output and causes a reflex increase in heart rate.

The purpose of the present study was to evaluate the utility of levosimendan after cardiac surgery. On the basis of the above-mentioned properties levosimendan should benefit haemodynamics and myocardial energetics after cardiac surgery.

### Methods

Twenty-three patients undergoing elective coronary artery bypass graft-surgery were enrolled in the investigation. All patients were men or surgically sterilized women under the age of 75 years with angiographically verified coronary artery disease and cineangiographically measured ejection fraction greater than 30%. Patients with significant valvular stenosis, second- or third-degree atrioventricular block, renal insufficiency (serum creatine >115 mmol. l⁻¹), abnormal liver function (serum albumin <30 g. l⁻¹), insulin-dependent diabetes mellitus or significant pulmonary disease or patients using antiarrhythmics or digoxin before the operation were excluded from enrolment. Patients with myocardial infarction, cerebral stroke or other major hospitalization within 3 months were also excluded.

Beta-blocking agents and short-acting nitrates were permitted prior to cardiopulmonary bypass, but not thereafter.

Angiotension converting enzyme inhibitors, calcium antagonists and long-acting nitrates were discontinued 24 h before beginning the study. All patients signed an informed consent form the day before the operation. The study protocol was approved by the Ethics Committee of the Third Department of Surgery and the Department of Anaesthesiology of Helsinki University Hospital. The study followed the guidelines of the Declaration of Helsinki.

From results of an open non-controlled pilot study the lower dose was selected as minimally haemodynamically effective and the higher dose as clearly haemodynamically effective, causing an approximately 20% increase in cardiac output. The patients were double-blindly randomized to receive placebo (PL, n=8), or 8 (LS1, n=8) or 24 μg. kg⁻¹ (LS2, n=7) of levosimendan administered as a 5-min infusion in a double-blind fashion. One patient was randomized to the LS2 group although he fulfilled one exclusion criterion (diabetes). Therefore he did not receive the study drug and was not included in the data analysis. For this reason the LS2 group is smaller than the other groups. The demographic data of the patients are shown in Table 1.

### Anaesthesia and cardiopulmonary bypass

In the operating room after premedication with morphin scopolamine, a radial arterial cannula and a pulmonary artery thermodilution catheter were inserted via the right jugular vein, and a separate introducer was placed in the internal jugular vein. Through the latter port a Wilton-Webster thermodilution coronary sinus catheter was inserted after cardiopulmonary bypass by the operating surgeon and anaesthesiologist. In the operating room, the exact position of the Wilton-Webster catheter in the coronary sinus was verified by flouroscopy, and small amounts of contrast media.

Electrocardiographic leads II and V₅ were monitored throughout the study. Cardiac output was
determined with thermodilution. Anaesthesia was induced with fentanyl and midazolam and maintained with infusions of midazolam (0.75 μg.kg⁻¹.min⁻¹) and fentanyl (0.15 μg.kg⁻¹.min⁻¹). The infusions were continued until the study interventions were over.

A membrane oxygenator with a roller pump and moderate systemic hypothermia were used for cardio-pulmonary bypass. Crystalloid cardioplegia was administered at an initial dose of 10 ml.kg⁻¹ after the aorta was cross-clamped. Subsequent doses of 2–3 ml.kg⁻¹ were administered to maintain electromechanical quiescence. Before separation from bypass, the patient was rewarmed to a rectal temperature of >35°C.

Measurements and calculations

Assessment of efficacy

Before the patient could finally be included in the study, he/she had to meet the following study initiation criteria: sinus rhythm, cardiac index >1·71.min⁻¹.m⁻², mean arterial pressure >60 mmHg, and pulmonary capillary wedge pressure (PCWP) 8–20 mmHg.

Coronary sinus flow was measured via thermodilution. Flow was determined by measurement of coronary sinus blood temperature (CF-300 Triple channel flowmeter, Webser Laboratories) during infusion of an isotonic saline solution at room temperature into the coronary sinus at a rate of 57·5 ml.min⁻¹, according to the method described by Ganz et al. [113].

The study was started approximately 30–60 min after perfusion by measuring coronary flow at 10 min intervals as many times as required — usually 2 to 4 times — so that the flow values from two consecutive measurements were within 25% of the mean. After measurement of coronary blood flow, mean arterial pressure, right atrial pressure, pulmonary arterial pressure, PCWP, and cardiac output were determined and an ECG recorded, the 5-min infusion of drug or placebo was then started. After cessation of drug or placebo infusion (0 min) coronary blood flow, mean arterial pressure, right atrial pressure, pulmonary arterial pressure, PCWP, and cardiac output were measured and an ECG recorded; the measurements were repeated thereafter at 10, 20, 30, 45 and 60 min after terminating the infusion.

Blood samples for determination of myocardial oxygen consumption were drawn 10 min before and at 0, 10, 30 and 60 min after the infusion. Blood samples for cardiac substrate (free fatty acids, glucose, lactate, and pyruvate) utilization were drawn 10 min before and 30 min after drug or placebo infusion. Blood samples for determination of pulmonary shunt fraction were obtained 10 min before and 10 min after drug or placebo infusion. ST segment was monitored continuously (60 ms after the J-point) from the ECG.

Calculations and formulas

Mean arterial pressure, stroke volume (ml), systemic vascular resistance (dyn.s⁻¹.cm⁻⁵) and pulmonary vascular resistance (dyn.s⁻¹.cm⁻⁵) were calculated from standard formulae. Coronary perfusion pressure (mmHg) was defined as diastolic arterial pressure (DAP) – PCWP, and coronary vascular resistance (dyn.s⁻¹.cm⁻⁵) as 80 × (DAP – PCWP)/coronary blood flow[141]. Oxygen content (ContO₂, ml O₂) was defined as oxygen saturation (SaO₂, %) × Hb (g.100 ml⁻¹) × 1·39/100, and myocardial oxygen consumption (ml oxygen/min) as coronary blood flow × (arterial ContO₂ – coronary sinus ContO₂) × 10⁻³. Extractions of myocardial substrates (FFA, glucose, lactate and pyruvate) were calculated as 100 × (arterial concentration – coronary sinus concentration)/arterial concentration and differences in oxygen contents (O2Diii) as differences between arterial and coronary sinus oxygen content. Pulmonary shunt fraction (%) was calculated as (CCO₂ – CAO₂)/(CCO₂ – CVO₂), where CCO₂=Hb concentration × 1·39 × 100 – (carbon monoxide+methemoglobin concentration)/100+0·031 × (356·6 – arterial pressure of carbon dioxide/0·8), CAO₂=arterial Hb concentration × 1·39 × arterial oxygen saturation/100+0·031 × arterial pressure of oxygen, and CVO₂=mixed venous Hb concentration × 1·39 × 12/100+0·031 × mixed venous partial pressure of oxygen. CCO₂, CAO₂ and CVO₂ refer to capillary, arterial and mixed venous oxygen contents in that order[15,16].

Statistical methods

Haemodynamic changes were analysed separately using a univariate repeated measures analysis of variance model, which included both random and fixed effects (mixed model). The treatment (three levels) and time (1, 4 or 6 levels depending on the response) were treated as fixed effects and patients as a random effect. The mean of the baseline measurements (obtained at 20, 10 and 5 min prior to drug/placebo infusion) was used as a covariate in the model. Estimates for the dose effects by time, the overall dose effects and for the average effect of levosimendan were calculated. Bonferroni correction was applied in the construction of the simultaneous 95% confidence intervals for the estimated effects. The number of timepoints by dose (e.g. 6 timepoints in Tables 2 and 3) was one factor adjusted by the Bonferroni correction. When effects for LS1-PL and LS2-PL were estimated, the confidence level of 1–0·05/6=0·0083 was applied at each timepoint. This corresponds to a P-value of 0·0083 for significance at each timepoint and dose level. The other factor adjusted by the Bonferroni correction was the number of doses when the overall dose effects were evaluated, i.e. a P-value of 0·025 was considered statistically significant. Statistical analyses were carried out using the MIXED procedure with SAS software[17,18].

Results

The overall effects of LS1 and LS2 0-60 min after drug infusions in comparison with placebo (PL) and also...
Table 2  Systemic haemodynamics (mean ± SEM) after 5-min infusions of placebo (PL, n=8), 8 (LS1, n=8) or 24 (LS2, n=7) µg . kg⁻¹ of levosimendan after coronary artery bypass grafting. 0 min = end of drug infusion

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*P<0.05 in comparison to placebo at individual time-points (in connection to the mean value) or when all observations after each treatment are grouped (brackets on the right). B = baseline, PCWP = pulmonary capillary wedge pressure.

Effects at individual time-points are presented with 95% confidence intervals in parentheses.

Patients (Table 1)

The placebo and LS1 and LS2 groups were similar in age, ejection fraction and number of diseased vessels. The only notable difference between the groups was the greater number of female patients in the placebo group: four out of eight vs one of eight and one of seven in LS1 and LS2 groups, respectively.

Systemic haemodynamics (Table 2, Fig. 1)

Heart rate increased significantly after LS2; the maximum effect of 11 beats . min⁻¹ was observed at time points 20, 30 and 45 min. An increase in cardiac output occurred after both doses of levosimendan. The increase in cardiac output was attributable to increases in stroke volume approximately 10 ml after LS2. The mean arterial pressure was significantly decreased (<10 mmHg) after both doses of levosimendan. After the higher dose, one patient had a decrease of mean arterial pressure to 54 mmHg 30 min after drug infusion. The peak effects of systemic vascular resistance were observed between 10 and 45 min after LS1. After LS2, the maximum decrease in systemic vascular resistance, by approximately 450 dyn . s⁻¹ . cm⁻⁵, was observed immediately after infusion. Pulmonary arterial pressure decreased similarly, but only by 2 mmHg after LS1 and LS2, but pulmonary vascular resistance decreased significantly after both doses of levosimendan. There were no significant changes in right and left ventricular filling pressures; right atrial pressure and PCWP remained at baseline after both doses of levosimendan. When the percent of pulmonary shunting was measured at baseline and 10 min after infusions, the change was from 23 to 19%, from 17 to 19% and, from 15 to 22% after placebo, LS1 and LS2, respectively. In comparison with placebo,
The difference of 10%\(^2\) after LS2 was statistically significant even though the baseline differences were taken into account.

**Coronary haemodynamics (Table 3, Fig. 1)**

The overall increase of coronary blood flow was 28 ml . min\(^{-1}\) (\(-22, 77\)) and 42 ml . min\(^{-1}\) (\(-8, 92\)) after LS1 and LS2, respectively. The average increase in coronary blood flow was 35 ml . min\(^{-1}\) (\(-1, 70\)) with a P-value of 0.0539 when both doses were combined in the analysis. Coronary vascular resistance and coronary perfusion pressure decreased significantly after both doses. The increase in myocardial oxygen consumption after levosimendan was not statistically significant. There were no significant changes in O\(_2\) Diff values after levosimendan.

**Myocardial substrate utilization (Fig. 2)**

No significant changes in myocardial substrate utilization were produced by levosimendan. Utilization of free fatty acid, lactate, pyruvate, and glucose remained the same. In the placebo group, four patients were producers of lactate at baseline and they changed to consumers of lactate at 30 min. Only one patient changed from consumer to producer. In the LS1 group, two patients changed from consumers to producers and two patients changed from producers to consumers. In the LS2 group, one patient changed from consumer to producer and one from producer to consumer. There were no differences between the groups.

The determination of plasma pyruvate was successful only four out of eight times in the placebo group, and in six out of seven in the high-dose group due to technical difficulties. All determinations in the low-dose group were successful. No significant differences were observed between groups.

**ST segments in ECG**

The mean values of ST segments in lead II were all between -0.1 and 0.2 mV and between -0.1 and 0.3 mV in lead V\(_5\). All changes being statistically non-significant. The most negative individual value of -0.8 mV was recorded at baseline in the V\(_5\) lead of one patient in the LS2 group, increasing to +0.2 mV after levosimendan.

Figure 1  Mean cardiac output (CO), coronary sinus blood flow (CBF), systemic vascular resistance (SVR), and myocardial oxygen consumption (MVO\(_2\)) after 5-min infusions of placebo (■, n=8), and 8 (●, n=8) and 24 µg . kg\(^{-1}\) (▲, n=7) of levosimendan after coronary artery bypass grafting. Grey bars indicate 5-min treatment infusions. B = baseline; data are shown with ± SEM. *P < 0.05 in comparison with placebo.
Figure 2  Extractions of free fatty acids, lactate, pyruvate, and glucose 10 min before (□) and 30 min (■) after 5-min infusions of placebo (PL), and 8 (LS1) or 24 µg · kg⁻¹ (LS2) of levosimendan after coronary artery bypass grafting. Values below the columns indicate number of observations. Data are shown with ± SEM.

Table 3  Coronary haemodynamics (mean ± SEM) after 5-min infusions of placebo (PL, n=8), 8 (LS1, n=8) or 24 (LS2, n=7) µg · kg⁻¹ of levosimendan after coronary artery bypass grafting. 0 min = end of drug infusion

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| **Coronary vascular resistance** (dyn · s⁻¹ · cm⁻¹) | PL    | 30±3 (30±6) | 32±5 (32±7) | 33±5 (33±7) | 31±5 (31±7) | 35±5 (35±7) | 35±5 (35±7) | *
|                          | LS1   | 28±2 (28±2) | 26±2 (26±2) | 23±2 (23±2) | 21±2 (21±2) | 22±2 (22±2) | 22±2 (22±2) | *
|                          | LS2   | 28±2 (28±2) | 20±2 (20±2) | 19±2 (19±2) | 22±2 (22±2) | 23±2 (23±2) | 22±2 (22±2) | *
| **Coronary perfusion pressure** (mmHg) | PL    | 50±1 (50±1) | 53±1 (53±1) | 51±1 (51±1) | 49±1 (49±1) | 48±1 (48±1) | 48±1 (48±1) | 50±1 (50±1) | *
|                          | LS1   | 59±1 (59±1) | 55±1 (55±1) | 49±1 (49±1) | 47±1 (47±1) | 48±1 (48±1) | 50±1 (50±1) | 52±1 (52±1) | *
|                          | LS2   | 54±1 (54±1) | 45±1 (45±1) | 41±1 (41±1) | 44±1 (44±1) | 45±1 (45±1) | 51±1 (51±1) | 50±1 (50±1) | *
| **O2Diff (ml O₂)**       | PL    | 5±1 (5±1) | 5±1 (5±1) | 5±1 (5±1) | 6±1 (6±1) | 6±1 (6±1) | 6±1 (6±1) | 6±1 (6±1) | *
|                          | LS1   | 6±1 (6±1) | 6±1 (6±1) | 5±1 (5±1) | 5±1 (5±1) | 5±1 (5±1) | 5±1 (5±1) | 6±1 (6±1) | *
|                          | LS2   | 5±1 (5±1) | 4±1 (4±1) | 4±1 (4±1) | 4±1 (4±1) | 4±1 (4±1) | 4±1 (4±1) | 5±1 (5±1) | *

*P <0.05 in comparison with placebo at individual time-points (in connection to the mean value) or when all observations after each treatment are grouped (brackets on the right). B = baseline, and O2Diff = difference of oxygen contents between arterial and coronary sinus blood.

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after administration of the high dose of levosimendan. There were no changes in the ECG suggesting that levosimendan would cause ischaemia.

Discussion

Findings and implications

On the basis of animal studies[10], we would have expected levosimendan to have more potent coronary vasodilating activity. A tendency towards an increase in coronary blood flow and a statistically significant decrease in coronary vascular resistance after the higher dose of levosimendan was observed. Coronary perfusion pressure decreased after both doses. Decreased perfusion pressure might have detrimental effects in myocardium supplied by a critically stenosed coronary artery[19]. Levosimendan may override normal autoregulatory vasodilatory mechanisms of coronary circulation and thus dilate coronary vessels more than myocardial metabolism would indicate. However, there were no ischaemic changes in lactate extractions or signs of ischaemia in ST-segment monitoring.

The proximity of revascularization and re-established perfusion probably affects coronary flow and the utilization of substrates in energy production in the myocardium. Svensson et al.[20] have reported that carbohydrates and lipids are not utilized early after coronary artery graft surgery and that amino acids are the only exogenous substrates taken up by the heart. A change towards normalization takes place over 4 h[21]. This transition probably did not occur in our patients during the one hour of follow-up. We found only minor changes in utilization of myocardial substrates after levosimendan and no evidence that levosimendan would increase free fatty acid utilization instead of lactate or glucose. Because the study was performed within 2 h of cardiopulmonary bypass, the changes in metabolism produced by coronary artery graft surgery are so great that a drug that does not directly affect adrenergic regulation and metabolism of the heart cannot change the substrate utilization in this situation[20,22]. Therefore, these results cannot be applied directly to normal metabolic situations. Furthermore, comparisons with the effects of other inotropes during other experimental conditions are difficult.

Systemic haemodynamics changed, as expected from previous studies with levosimendan[11,12,23]. The increase in cardiac output after 24 μg kg⁻¹ of levosimendan was related to increases in heart rate and stroke volume, as demonstrated in previous studies with levosimendan[23]. This phenomenon is typical of almost all inotropic and vasodilating compounds in acute intravenous use. In chronic treatment, an increase in heart rate did not occur. This is similar to another inotropic compound, pimobendan, which does not increase heart rate during long-term treatment[24,25], although it increases heart rate in acute intravenous use more than does doxosimendan[24-27]. In the present study, the increase in heart rate after the higher dose of levosimendan was of the same magnitude as after efficacious doses of milrinone, amrinone, enoximone and dubutamine[15,28-30].

Like other drugs with potent vasodilating activity, levosimendan increased intrapulmonary shunting. Excessive intrapulmonary shunting may decrease arterial oxygen saturation, as has been reported with amrinone[15], and cause hypoxia of myocardium and peripheral tissues[19]. This effect was not observed after levosimendan in this study as the increase in shunting was relatively small and the arterial oxygen saturation not compromised.

Most patients had beta-blocking agents, long-acting nitrates or calcium-antagonists in their concomitant medication. Only short-acting nitrates were used before surgery, but not thereafter. Concomitant medications may have had an impact on haemodynamic responses but they probably did not confound the comparisons between groups because their effects were evenly distributed amongst the groups. The placebo and levosimendan groups were very similar in respect to demographic data and severity of coronary artery disease, the only difference was the greater number of female patients in the placebo group, which may have resulted in a lower baseline coronary blood flow value in this group.

The present study was the first in which the effects of a calcium sensitizer were evaluated after cardiac surgery. Overall the haemodynamic effects of levosimendan are similar to those of other inotropes during experimental conditions: increases in heart rate, cardiac index and stroke volume, and decreases in peripheral resistance and pulmonary perfusion pressure. Despite the favourable haemodynamic actions, levosimendan did not increase myocardial oxygen consumption, unlike the PDE inhibitors enoximone and R 80122, or dobutamine[31,32]. All these drugs have been shown to increase intrapulmonary shunting, to the same or even greater extent, as compared to levosimendan in the present study.

Limitations

Patients received crystalloid or colloid solutions before and during the study, which probably prevented filling pressures from decreasing. In a previous investigation, levosimendan has been shown to decrease filling pressures profoundly[11]. Mean arterial pressure and systemic vascular resistance decreased, reflecting the systemic vasodilating potential of levosimendan. In clinical situations, a profound decrease in blood pressure might require use of vasoconstricting drugs in conjunction with levosimendan. On the other hand, moderate decreases in systemic vascular resistance are desirable, reducing impedance to left ventricular ejection.

Thermodilution is a widely used and accepted technique for measuring coronary blood flow in man[13,14,33]. However, the technique has certain
limits. It is highly dependent on the anatomical conditions in the coronary sinus; even a small movement of the tip of the catheter can affect measured flow values. In the present study, the site of the catheter was confirmed with fluoroscopy. Because the patients were anaesthetized, spontaneous movement did not alter the site of the catheter. Although most of the patients were moved from the operating room to the recovery room after fluoroscopy, there were no changes in their position after the first measurement. The mean of coefficient of variation calculated from the measurements of coronary sinus blood flow before drug infusion was 6.2% (range from 0.4 to 15.4%), which can be considered acceptable.

The patients included in this study represent a population with a good prognosis for coronary artery bypass graft surgery. They had good left ventricular function and those with substantial difficulties during the surgical procedure because of low output were excluded from the study before randomization. Thus, the present results may not be directly applicable to patients who could potentially benefit from the administration of levosimendan. It is noteworthy that after digoxin myocardial oxygen requirements increased in patients without heart failure but not in those with heart failure.

Conclusions

Levosimendan increased cardiac output and stroke volume and decreased systemic vascular resistance without increasing myocardial oxygen consumption or causing myocardial substrate utilization to deteriorate. On the basis of the present results, levosimendan may be a beneficial drug in low output states after cardiopulmonary bypass.

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