The Effects of Levosimendan in Cardiac Surgery Patients with Poor Left Ventricular Function

Stefan G. De Hert, MD, PhD*
Suraphong Lorsomradee, MD*
Stefanie Cromheecke, MD*
Philippe J. Van der Linden, MD, PhD†

BACKGROUND: Patients with poor left ventricular function often require inotropic drug support immediately after cardiopulmonary bypass. Levosimendan improves cardiac function by a novel mechanism of action compared to currently available drugs. We hypothesized that, in patients with severely compromised ventricular function, the use of levosimendan would be associated with better postoperative cardiac function than with inotropic drugs that increase myocardial oxygen consumption.

METHODS: Thirty patients with a preoperative ejection fraction \( \leq 30\% \) scheduled for elective cardiac surgery with cardiopulmonary bypass were randomized to two different inotropic protocols: milrinone 0.5 mg \( \text{kg}^{-1} \text{min}^{-1} \) or levosimendan 0.1 mg \( \text{kg}^{-1} \text{min}^{-1} \), started immediately after the release of the aortic cross clamp. The treatment was masked to the observers. All patients received dobutamine 5 mg \( \text{kg}^{-1} \text{min}^{-1} \).

RESULTS: Stroke volume was similar between groups initially after surgery, but it declined 12 h after surgery in the milrinone group but not in the levosimendan group \( (P < 0.05 \text{ between groups}) \) despite similar filling pressures. Total dose, duration of inotropic drug administration and norepinephrine dose were lower in the levosimendan group than in the milrinone group \( (P < 0.05) \). The duration of tracheal intubation was shorter in the former group compared with the milrinone group \( (P = 0.008) \). Three patients in the milrinone group but none in the levosimendan group died within 30 days of surgery.

CONCLUSION: In cardiac surgery patients with a low preoperative ejection fraction, stroke volume was better maintained with the combination of dobutamine with levosimendan than with the combination of dobutamine with milrinone.

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Patients with poor left ventricular function undergoing cardiac surgery frequently require inotropic drug support immediately after cardiopulmonary bypass (CPB). Indeed, preexisting impaired ventricular function is further compromised by variable degrees of myocardial stunning and/or myocardial injury resulting from ischemia during aortic crossclamping. Currently available inotropic drugs enhance myocardial contractility by increasing cyclic adenosine monophosphate concentrations, which ultimately increases the myocardial concentrations of calcium. This effect is associated with an increase in myocardial oxygen consumption, which may further alter the already compromised myocardial oxygen balance in patients with preexisting ventricular dysfunction.

Levosimendan is a novel compound with a unique mechanism of action (1,2). By binding to cardiac troponin C, levosimendan enhances myofilament responsiveness to calcium, thereby increasing myocardial contraction without increasing myocardial oxygen consumption (3–5). In addition, levosimendan activates K\(_{\text{ATP}}\) channels which are important mediators of ischemic and anesthetic cardioprotection (6). Levosimendan might thus have a potential benefit for patients with myocardial oxygen imbalance requiring inotropic drug support.

To address this question, we conducted a prospective single-institutional study. We hypothesized that in patients with left ventricular dysfunction, the combination of levosimendan with dobutamine would result in better postoperative cardiac function after cardiac surgery than the combination of dobutamine with the phosphodiesterase III inhibitor milrinone.

METHODS

Patient Population

The study was approved by the Institutional Ethical Committee (University Hospital Antwerp, Edegem, Belgium), and written informed patient consent was
obtained. Thirty consecutive patients with preoperative left ventricular ejection fraction \( \leq 30\% \) scheduled for elective cardiac surgery with CPB were enrolled.

**Study Groups**

Patients were randomly allocated to one of two post-CPB inotropic protocols, using a computer-generated random code. The participant randomization assignment was concealed in an envelope until after anesthesia induction. The observers were blinded to the inotropic protocol. Caregivers were not blinded, but they did not participate in data collection or data interpretation.

Both groups received dobutamine (Dobutamine\textsuperscript{®}; Eumedica, Manage, Belgium) 5 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) beginning when the core body temperature was 33°C during rewarming on CPB. In addition, patients received either milrinone (Corotrope\textsuperscript{®}; Sanofi Synthelabo, Brussels, Belgium) 0.5 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) or levosimendan (Simdax\textsuperscript{®}; Abbott, Luxembourg, Luxemburg) 0.1 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) started immediately after the release of the aortic crossclamp. According to our standard practice, no bolus dose of either drug was administered because of concern for severe hypotension associated with the bolus dose of either drug.

**Anesthesia and Perioperative Procedures**

All preoperative cardiac medication was continued until the morning of surgery, except for angiotensin-converting enzyme inhibitors, which were stopped the day before surgery and aspirin, which was stopped 5 days before surgery because of the concern of postoperative bleeding. The patients were premedicated with 2.5 mg sublingual lorazepam (Temesta Expidet\textsuperscript{®}; Sanofi Synthelabo, Paris, France) followed by a concentration of 2% until intubation. The patients received routine monitoring including pulmonary artery catheters with continuous cardiac output measurement (Swan Ganz CCO/VIP, Edwards Lifesciences LLC, Irvine, CA) and bispectral index monitoring (BIS A2000 system, Aspect Medical Systems, Newton, MA). Anesthesia was induced with remifentanil (Ultiva\textsuperscript{®}; Glaxo Smith Kline, Genval, Belgium) 0.3 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) and sevoflurane (Sevorane\textsuperscript{®}; Abbott, Louvain-la-Neuve, Belgium) 8% for 5 breaths followed by a concentration of 2% until intubation. Muscle relaxation was obtained with 0.15 mg/kg cisatracurium (Nimbex\textsuperscript{®}; Glaxo Smith Kline) followed by 0.03 mg/kg every 60 min. Anesthesia was maintained with remifentanil 0.2–0.4 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) and sevoflurane 0.5%–1%. The concentrations of the anesthetics were titrated to maintain a bispectral index <50 throughout the procedure. During CPB, anesthesia was maintained with remifentanil (0.2–0.4 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \)) and sevoflurane (0.5%–1% measured at the outlet of the oxygenator).

The patients included in the study were managed by two experienced cardiothoracic anesthesiologists and three experienced surgeons, using the same surgical technique. The cardioprotective strategies included the use of a volatile anesthetic regimen, 2 g methylprednisolone after anesthesia induction. A bolus dose of 2 \( \times \) 10\(^5\) kallikrein inhibiting units of aprotinin (Trasyrol\texttrademark; Bayer, Leverkusen, Germany) was given followed by a continuous infusion of 5 \( \times \) 10\(^4\) kallikrein inhibiting units/h until the end of CPB. The CPB circuit was a closed surface system with a modified additive coating system and a hollow fiber membrane oxygenator (Cobe Cardiovascular Inc., Arvada, CO). The priming fluid of the CPB circuit contained 1000 mL 6% hydroxyethyl starch 130/0.4 (Voluven\textsuperscript{®}, Fresenius Kabi, Schelle, Belgium), 300 mL crystalloids (Plasma-Lyte\textsuperscript{®}, Baxter, Lessines, Belgium), 5000 U of heparin. Nonpulsatile CPB flow was kept between 2.2 and 2.5 L \( \cdot \) min\(^{-1} \) \( \cdot \) m\(^{-2} \) and mean perfusion pressure between 50–60 mm Hg. During CPB, the patient’s body temperature was maintained between 30°C and 32°C and the hematocrit was kept between 20% and 25%. Revascularization was performed using intermittent aortic crossclamping. In the case of valve or combined coronary artery and valve surgery, cold crystalloid cardioplegic solution (Custadiol\textsuperscript{®}; HTK-Bretschneider solution for cardioplegia, Dr Franz Köhler Chemie GMBH, Alsbach-Hähnlein, Germany) was given. Lidoflazine (a nucleoside transport inhibitor), 1 mg/kg (Johnson and Johnson, Beerse, Belgium) was given for coronary artery surgery patients.

At the end of the surgical procedure, the reperfusion of the heart was performed for at least 50% of the total aortic crossclamping time. The patient’s body was rewarmed to a bladder temperature of 35°C, the heart was paced using an atrioventricular sequential mode at 90 bpm. After separation from CPB and removal of the aortic cannula, heparin activity was neutralized with protamine sulfate (Protamine\textsuperscript{®}; Leo Pharma, Zaventem, Belgium) at a ratio of 1 mg protamine for 100 U of the total heparin given. Protamine administration was further guided by activated clotting time measurements aiming at a value of 140 s. At the end of the surgical procedure, patients were transferred to the intensive care unit (ICU).

**Inotrope and Vasoactive Drug Therapy**

In all patients, the central venous pressure was kept between 12 and 14 mm Hg and pulmonary capillary wedge pressure 15 and 18 mm Hg by administration of IV fluids (crystalloids and colloids). If the cardiac index was below 2.5 L \( \cdot \) m\(^{-2} \) \( \cdot \) min\(^{-1} \), dobutamine was increased to a maximum of 10 mg \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \). Concentrations of milrinone or levosimendan were kept constant until weaning from inotropic support. Higher infusion rates of both drugs were not administered to avoid the risk of severe hypotension associated with higher concentrations. Hypotension, defined as a mean arterial blood pressure <60 mm Hg, was treated with...
norepinephrine 0.1 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) increased incrementally by 0.1 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) until the mean arterial blood pressure was \( \geq 60 \) mm Hg.

Weaning from inotropic drug support was at the discretion of the responsible anesthesiologist in the ICU and was based on the assessment of hemodynamic data, urine output, and the patient’s physical status. These physicians were not involved in the collection or the interpretation of the study data.

**Hemodynamic Data Analysis**

Hemodynamic data were obtained before the start of surgery (base), 15 min after separation from CPB (post-CPB), at the end of the operation (end surgery), on arrival in the ICU (T0), and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) h later. Cardiac output was measured in triplicate at end-expiration by thermodilution using 10 mL of iced saline.

**Transfusion Protocols**

Transfusion of packed red blood cells aimed for a hemoglobin between 7 and 10 g/dL guided by clinical judgment (age, estimated blood volume, cardiovascular and respiratory functions), and postoperative bleeding (7). Platelets and fresh frozen plasma were transfused in the presence of abnormal clinical bleeding, using the algorithm developed by Despotis et al. (8), based on the platelet count, and prothrombin and partial thromboplastin times.

**Extubation and Discharge Protocols**

Patients were sedated for 2 h with remifentanil 0.3–0.5 mg \( \cdot \) kg\(^{-1}\) \( \cdot \) h\(^{-1}\) and propofol 0.5 mg \( \cdot \) kg\(^{-1}\) \( \cdot \) h\(^{-1}\) until hemodynamic variables and temperature were stable and there were no signs of excessive bleeding (>150 mL/h). Weaning from mechanical ventilation and tracheal extubation followed a standard protocol using the following criteria: temperature \( \geq 36^\circ\)C, stable hemodynamics (defined as the ability to increase body oxygen consumption (e.g., spontaneous breathing) without the need for increased inotropic support), chest tube drainage <100 mL/h, and urine output \( \geq \) 0.5 mL \( \cdot \) kg\(^{-1}\) \( \cdot \) h\(^{-1}\). Patients received morphine 0.2 mg/kg and paracetamol 1 g (Perfusalan\(^\text{\textregistered}\), Bristol-Myers Squibb, Waterloo, Belgium) and propofol was stopped. Fifteen minutes later, remifentanil was reduced in 10-min intervals. If the patients experienced pain, 5 mg morphine was administered. The patient’s trachea was extubated when the following criteria were achieved: adequate response to command, \( \text{SpO}_2 \geq 95\% \) at \( \text{FiO}_2 \leq 0.5, \) pH \( \geq 7.3, \) \( \text{Paco}_2 \leq 55 \) mm Hg, and respiratory rate <30 bpm.

Patients were discharged from the ICU when the following criteria were met: \( \text{SpO}_2 \geq 90\% \) at \( \text{FiO}_2 \leq 0.5 \) by facemask, stable hemodynamics, chest tube drainage <50 mL/h, urine output >0.5 mL \( \cdot \) kg\(^{-1}\) \( \cdot \) h\(^{-1}\), no IV inotropic or vasopressor therapy.

The criteria for hospital discharge were hemodynamic and cardiac rhythm stability, no incisional drainage, no temperature, the ability to void and move bowels, and ability to independently ambulate and self-feed.

**Data Collection and Analysis**

Data were collected by trained observers who did not participate in patients’ care and were blinded to the inotropic regimen. Risk stratification was performed using the EuroSCORE (9). Blood was obtained from all patients for analysis of troponin I, creatine kinase (total + MB fraction), glutamic oxaloacetic transferase (SGOT), glutamic pyruvate transferase (SGPT), lactic dehydrogenase (LDH), and serum creatinine. These samples were obtained before surgery (preoperative), on arrival in the ICU (T0), after 6 (T6), 12 (T12), 24 (T24), and 48 h (T48). In addition to demographic and clinical information, other data recorded include: myocardial infarction, defined as the occurrence of new Q wave or new persistent ST segment or T-wave changes on daily 12-lead electrocardiogram; atrial fibrillation; the duration of tracheal intubation; the amount of chest tube drainage; the need for blood transfusion; any other adverse event; and the duration of hospitalization in the ICU and on the postoperative ward.

**Statistical Analysis**

The primary outcome variable was stroke volume index at T24. A minimum detected difference in stroke volume index of 5 mL/m\(^2\) between groups was considered clinically significant. We calculated that a sample size of 14 patients was necessary to detect a difference of this variable between treatment groups with a power of 0.9 and \( \alpha = 0.05 \).

Statistical analysis was performed using the SigmaStat 2.03 software package (SPSS, Leuven, Belgium). Patient characteristics and postoperative complications between groups were compared using one-way analysis of variance and \( \chi^2 \) analysis where appropriate.

After testing for normal distribution data were compared using a two-way analysis of variance for repeated measurements. Interaction analysis revealed whether effects of time (repetitive measurements) were different between groups. Post-test analysis was performed using the Bonferroni-Dunn test. All hemodynamic and biochemical data were expressed as mean \( \pm \) sd. When data were not normally distributed, groups were compared with the Mann-Whitney ranked sum test and expressed as median with range. Statistical significance was accepted at \( P < 0.05 \). All \( P \) values were two-tailed.

**RESULTS**

Patient characteristics are summarized in Table 1. There were no differences between groups in any of the pre- or intraoperative data. Hemodynamic data are listed in Table 2 and stroke volume index data are shown in Figure 1. Heart rate, central venous pressure,
Intraoperative data

- CABG procedure: 4 vs. 5
- Valve procedure:
  - Aortic valve: 1 vs. 1
  - Mitral valve: 2 vs. 2
- Combined CABG + valve procedure: 8 vs. 7
- No. of bypass grafts in CABG (median (range)): 3 (2–4) vs. 4 (3–5)
- CPB time (min): 134 ± 36 vs. 129 ± 33
- Aortic cross-clamp time (min): 79 ± 42 vs. 77 ± 33

Data are mean ± SD, unless stated otherwise.

LV = left ventricular; ACE = angiotensin converting enzyme; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass. There were no differences between the two groups in any of the pre- and intraoperative patient characteristics.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Milrinone (n = 15)</th>
<th>Levosimendan (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>69 ± 10</td>
<td>67 ± 11</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m^2)</strong></td>
<td>26.2 ± 3.7</td>
<td>26.3 ± 3.6</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>27 ± 3</td>
<td>24 ± 6</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>12.6 (5.6–23.1)</td>
<td>12.7 (8.4–35.6)</td>
</tr>
<tr>
<td><strong>Logistic EuroSCORE (median (range))</strong></td>
<td>18 (11–26)</td>
<td>19 (12–27)</td>
</tr>
<tr>
<td><strong>Chronic preoperative medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Nitrates</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Diuretics</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Digoxine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

and mean arterial blood pressure were not different between groups as a result of cardiac pacing and adherence to the protocol for maintaining these variables within specified ranges. The total amount of fluids administered intraoperatively and during the first 24 h postoperatively was similar in both groups (102 ± 16 mL/kg in the milrinone group and 98 ± 14 mL/kg in the levosimendan group). Intraoperative and postoperative blood loss was also similar in both groups (18 ± 11 and 19 ± 10 mL/kg respectively). Although postoperative stroke volume index was initially similar between groups, it was decreased at T12, T24, and T48 in the milrinone group compared with the levosimendan group. Duration of study drug administration was 19 ± 4 h in the levosimendan group compared with 83 ± 39 h in the milrinone group (P < 0.001). In all patients in the levosimendan group, the drug could be stopped within the first 24 h after the start of the infusion. The total dose and duration of administration of dobutamine and norepinephrine were lower in the levosimendan group (Table 3). Four patients in each group had an intraaortic balloon pump inserted preoperatively. Duration of mechanical inotropic support was shorter in the levosimendan group.
The intensive care unit (T0), and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) h later in both groups. Data are mean ± sd.

*Statistically significant difference between groups for \( P < 0.05 \).

![Figure 1. Stroke volume (SVI) at the start of surgery (base), 15 min after the end of cardiopulmonary bypass (CPB) (post-CPB), at the end of the operation (end surgery), at arrival in the intensive care unit (T0), and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) h later in both groups. Data are mean ± sd.

Table 3. Inotropic and Vasopressor Medication

<table>
<thead>
<tr>
<th></th>
<th>Milrinone (( n = 15 ))</th>
<th>Levosimendan (( n = 15 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>10.89 ± 4.755</td>
<td>31.13 ± 2.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total dose (( \mu g/kg ))</td>
<td>34 ± 9</td>
<td>15 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time (h)</td>
<td>19.13 ± 8.660</td>
<td>11.18 ± 2.883</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. patients</td>
<td>15</td>
<td>15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study medication</td>
<td>1318 ± 1304</td>
<td>115 ± 62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total dose (( \mu g/kg ))</td>
<td>83 ± 39</td>
<td>19 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IABP</td>
<td>171 ± 55</td>
<td>41 ± 22</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

IABP = intraaortic balloon pump; CPB = cardiopulmonary bypass.

Table 4. Biochemical Data

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
<th>T24</th>
<th>T48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I (ng/mL)</td>
<td>0.13 ± 0.27</td>
<td>2.06 ± 1.56*</td>
<td>3.97 ± 4.33*</td>
<td>4.95 ± 4.27*</td>
<td>4.71 ± 4.02*</td>
<td>4.16 ± 2.24*</td>
</tr>
<tr>
<td>Milrinone</td>
<td>0.12 ± 0.28</td>
<td>2.29 ± 1.52*</td>
<td>3.08 ± 2.40*</td>
<td>3.62 ± 2.25*</td>
<td>3.58 ± 2.35*</td>
<td>2.89 ± 1.65*</td>
</tr>
<tr>
<td>CK (U/mL)</td>
<td>66 ± 60</td>
<td>372 ± 178*</td>
<td>513 ± 292*</td>
<td>589 ± 172*</td>
<td>614 ± 185*</td>
<td>476 ± 159*</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>73 ± 34</td>
<td>372 ± 155*</td>
<td>434 ± 156*</td>
<td>478 ± 170*</td>
<td>474 ± 140*†</td>
<td>369 ± 93*†</td>
</tr>
<tr>
<td>CK-MB (U/mL)</td>
<td>3 ± 2</td>
<td>61 ± 24*</td>
<td>69 ± 36</td>
<td>73 ± 39*</td>
<td>63 ± 34*</td>
<td>33 ± 24*</td>
</tr>
<tr>
<td>Milrinone</td>
<td>3 ± 4</td>
<td>67 ± 27*</td>
<td>74 ± 30</td>
<td>73 ± 29*</td>
<td>47 ± 14*</td>
<td>26 ± 14*</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>31 ± 14</td>
<td>48 ± 11*</td>
<td>73 ± 47*</td>
<td>80 ± 31*</td>
<td>78 ± 19*</td>
<td>65 ± 17*</td>
</tr>
<tr>
<td>SGOT (U/mL)</td>
<td>29 ± 8</td>
<td>54 ± 15*</td>
<td>67 ± 32*</td>
<td>81 ± 31*</td>
<td>64 ± 16*†</td>
<td>45 ± 11*†</td>
</tr>
<tr>
<td>Milrinone</td>
<td>32 ± 14</td>
<td>47 ± 13*</td>
<td>49 ± 9*</td>
<td>54 ± 11*</td>
<td>51 ± 11*</td>
<td>49 ± 13*</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>31 ± 12</td>
<td>45 ± 10*</td>
<td>50 ± 11*</td>
<td>42 ± 12*</td>
<td>38 ± 7*†</td>
<td>35 ± 7*†</td>
</tr>
<tr>
<td>LDH (U/mL)</td>
<td>625 ± 170</td>
<td>767 ± 141*</td>
<td>1010 ± 318*</td>
<td>1135 ± 301*</td>
<td>1187 ± 275*</td>
<td>1110 ± 321*</td>
</tr>
<tr>
<td>Milrinone</td>
<td>605 ± 131</td>
<td>744 ± 173*</td>
<td>834 ± 166*</td>
<td>895 ± 127*†</td>
<td>800 ± 143*†</td>
<td>667 ± 112*†</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.05 ± 0.23</td>
<td>0.91 ± 0.21</td>
<td>0.99 ± 0.20</td>
<td>0.98 ± 0.21</td>
<td>1.00 ± 0.25</td>
<td>1.07 ± 0.32</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>1.28 ± 0.49</td>
<td>1.01 ± 0.43</td>
<td>1.08 ± 0.34</td>
<td>1.08 ± 0.38</td>
<td>1.08 ± 0.44</td>
<td>1.11 ± 0.44</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

CK = creatine kinase, CK-MB = creatine kinase cardiac muscle isoenzyme, SGOT = serum glutamic oxaloacetic transferase, SGPT = serum glutamic pyruvate transferase, LDH = lactic dehydrogenase.

*Statistically significant difference compared to base (\( P < 0.05 \)).
†Statistically significant difference between milrinone and levsimendan (\( P < 0.05 \)).

Perioperative troponin I levels, other cardiac isoenzyme levels and biochemical data are listed in Table 4. With the exception of creatinine, all of these values were significantly increased after surgery compared with baseline measurements. By T48, the different laboratory data had mostly returned to baseline values in the levsimendan group but not in the milrinone group. There were no differences between groups in cardiac troponin I, CK-MB, other cardiac enzymes at any measurement point.

Postoperative outcome data are listed in Table 5. The duration of tracheal intubation was longer in the milrinone group compared with the levsimendan group. The duration of hospitalization in the ICU and on the postoperative ward was not different between groups. Three patients in the milrinone group but none in the levsimendan group died within 30 days of surgery in the hospital (two patients as a cause of multiple organ failure on the 25th and the 38th postoperative day [mitral valve replacement (EuroSCORE =
Dobutamine day [aortic valve replacement (EuroSCORE patient because of cardiac failure on the 4th postoperative day] occurred in 71% to 100% of patients (12). In our institution, separation from CPB in such patients is typically performed with the combination of dobutamine and milrinone. Beta-adrenergic agonists such as dobutamine, and phosphodiesterase III inhibitors such as milrinone enhance myocardial contractility by increasing the concentration of cyclic AMP, and thereby intracellular calcium. This action results in an increase in myocardial oxygen consumption. In contrast levosimendan improves myocardial contractility primarily by enhancing myocardial contractile protein sensitivity to calcium without increasing its intracellular concentration. This action does not result in an increase in myocardial oxygen consumption (3–5). Levosimendan may, therefore, have a more advantageous profile than phosphodiesterase III inhibitors, especially in patients with a compromised myocardial oxygen balance.

The clinical effects of levosimendan have been documented in patients with decompensated low output heart failure. In these patients, levosimendan was shown to have advantages over current inotropic therapy, including prolonged drug effect after a single infusion, absence of complicating cardiac arrhythmias and lack of episodes of drug-induced myocardial ischemia (13–20). Some data suggest that this effect might also be related to antiinflammatory and antiapoptotic properties (21). In patients with left ventricular failure resulting from acute coronary artery syndromes, levosimendan has been shown to improve cardiac performance compared to a

### DISCUSSION

The main observation of the present study was that in cardiac surgery patients with low preoperative ejection fraction, stroke volume index was better maintained with the combination of dobutamine and levosimendan than with the combination of dobutamine and milrinone.

Variable degrees of postoperative myocardial stunning occur after cardiac surgery, even with the use of contemporary cardioprotective strategies. This may result in transient myocardial dysfunction, which is more pronounced in patients with impaired left ventricular function before surgery, resulting in the need for postoperative inotropic support (10,11). In patients with a left ventricular ejection fraction below 46%, for example, the need for inotropic support after surgery
placebo group (22–25). Finally, levosimendan has been used successfully in the treatment of cardiogenic shock or after postcardiotomy heart failure (2,4,26–30). However, in these latter reports levosimendan was used as rescue therapy, compared with placebo, or evaluated as the sole therapy for low cardiac index after CPB. The effects of levosimendan on postoperative cardiac function in patients with markedly reduced left ventricular function is considered good clinical practice, has not been previously demonstrated. Of note, both phosphodiesterase III inhibitors (31) and levosimendan, were reported to enhance the effects of dobutamine (6).

In addition to its calcium-sensitizing properties, levosimendan exhibits phosphodiesterase III inhibiting properties (1). This effect, however, is predominantly observed at higher concentrations and is less pronounced at concentrations in the clinically recommended therapeutic range. Levosimendan opens both mitochondrial and sarcolemmal $K_{ATP}$ channels, channels implicated in the mediation ischemic preconditioning (32). Experimental studies have indicated that levosimendan may protect the ischemic myocardium when administered before and during myocardial ischemia (33). One recent study has reported a myocardial preconditioning effect of levosimendan in coronary surgery patients (34).

A number of methodological issues should be considered with respect to the present observations. First, this study aimed to compare recovery of left ventricular function after cardiac surgery using two distinct well-defined inotropic protocols, which were randomly allocated to patients with a comparable risk profile, as apparent from the EuroSCORE and the preoperative characteristics. Our inclusion of patients undergoing all types of cardiac surgery might imply that the underlying cardiac pathophysiology might have differed among patients within the two groups. However, the distribution of the different cardiac interventions (coronary artery surgery, valve, or combined operation) was similar in both groups.

Data were collected and analyzed by observers who were blinded to the randomly assigned inotropic drug protocol. Caregivers were not blinded to the drug assignment, but they did not participate in the data collection or analysis. Much of the postoperative patient care was left to the discretion of the intensivist who used standard strategies for the weaning of inotropic drug support. Nonetheless, unblinding of the patient caregivers might have introduced a confounding factor that could have resulted in some minor differences in drug-weaning strategies.

Both milrinone and levosimendan were administered without the use of an initial loading dose. A main adverse effect of both drugs is the occurrence of hypotension. It has therefore been suggested that the initial loading be reduced or even to omitted (35,36), which has become common practice in our department. Reperfusion time in this study was set at 50% of aortic crossclamp time, which allowed the study drug sufficient time to circulate in the body.

Although the preoperative risk stratification and the intraoperative patient variables included were similar between groups, the present study was not powered to address patient outcomes. Experimental reports have observed an increased blood flow with levosimendan to various tissues including the gastric mucosa, the renal medulla, the small intestine, and the liver (37,38). Levosimendan seems superior to milrinone and dobutamine in selectively increasing microvascular gastric mucosal oxygenation (38,39), and it increases portal venous blood flow and oxygen delivery in experimental septic shock (40). Finally, improvement of renal function was observed with levosimendan compared with dobutamine in patients with low-output heart failure (15).

In conclusion, the results of the present study indicate that in cardiac surgery patients with a low preoperative ejection fraction, stroke volume was better maintained with the combination of dobutamine and levosimendan than with the combination of dobutamine and milrinone.

REFERENCES


