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Levosimendan as a New Strategy During Off-pump Coronary Artery Bypass Grafting: Double-blind Randomized Placebo-controlled Trial

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Aim To determine if levosimendan could improve cardiac performance during off-pump coronary artery bypass grafting in patients with normal preoperative left ventricular function.

Methods Twenty-four patients included in this double-blind randomized controlled trial received either placebo (n = 12) or 12 μg/kg loading dose of levosimendan (n = 12) during a period of 15 minutes before the surgery. The heart rate, cardiac index, stroke volume index, and left ventricular ejection fraction were measured before and 10 and 60 minutes after the drug administration.

Results The baseline measurements of hemodynamic parameters did not differ between the groups. Heart rate was not significantly different between the placebo and levosimendan group. Compared with placebo group, cardiac index and left ventricular ejection fraction were significantly higher 10 and 60 minutes ($p = 0.018$ for all) after administration of levosimendan. After 60 minutes, the cardiac index increased from the baseline value of 2.18 to 2.84 L/min/m^2. Left ventricular ejection fraction increased by 14% after 10 minutes, and by 10% after 60 minutes. Stroke volume index was significantly higher at 10 minutes ($p = 0.018$), but not at 60 minutes ($p = 0.063$) after the administration of levosimendan.

Conclusion Administration of 12 μg/kg of levosimendan enhances the left ventricular performance and offers a promising therapeutic option during off-pump coronary artery bypass grafting in patients with good preoperative left ventricular function.

During conventional coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB), the development of systemic inflammatory response syndrome, hypothermia, formation of microemboli, and desensitization of beta-adrenoceptors could extend postoperative recovery (1,2). On the other side, off-pump coronary artery bypass grafting (OPCABG) achieves better inhospital outcomes, similar completeness of revascularization, and shorter lengths of stay compared with conventional CABG (3,4).

Heart displacement during OPCABG is necessary to expose target coronary arteries. This manipulation of the beating heart, especially on the lateral and posterior left ventricular wall, may cause significant fluctuation in the patient's hemodynamic state (5,6). The major cause of hemodynamic changes is transitory biventricular systolic and diastolic dysfunction, and disturbance of diastolic filling of the right ventricle, primarily by direct ventricular compression (7). Inotropic support and use of vasoconstrictors are frequently es-

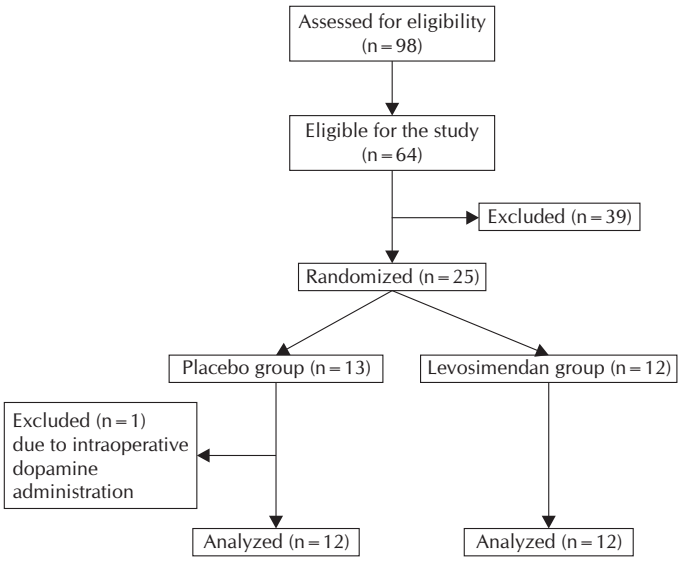

Figure 1. The flow diagram of patients through the study.

sential for the myocardial dysfunction after episodes of ischemia (stunning) during coronary occlusion. The myocardial stunning is related with decreased myofibril calcium sensitivity (8). Prophylactic usage of inotropic agents seems to be reasonable in this setting for patients undergoing OPCABG with normal left ventricular (LV) function (9,10).

Levosimendan is a new calcium sensitizer, which induces contractility by binding to troponin C without increasing intracellular calcium concentration. It has vasodilatatory and antiischemic properties attributable to its effects on adenosine triphosphate-dependent potassium channels. It also lowers the possibility of stunning and arrhythmias, and has neutral effect on myocardial energy (11,12). Until now, only two clinical prospective studies in CABG surgery have shown beneficial hemodynamic effects of levosimendan in patients with normal LV function (13,14).

The aim of our study was to determine if levosimendan could produce beneficial prolonged effects on left ventricular systolic function during OPCABG in patients with normal LV function.

Patients and Method

Patients

Out of 98 patients admitted to the Department of Anesthesiology, Reanimatology and Intensive Care, University Hospital Dubrava, Zagreb, between January 5, 2004, and the April 30, 2004, 64 patients were eligible for the study as they had the diagnosis of coronary artery disease. Out of 64 eligible patients, 25 met the inclusion criteria and were randomized into two groups (Fig. 1). The inclusion criteria were as follows: the degree I or II of Cardiac Anesthesia Risk Evaluation score (15), angiographically verified coronary artery disease, and left ventricular ejection fraction (EF) ≥50%. All patients were male and younger than 70 years of age (Table 1). Patients were excluded from the study if they had any kind of heart disease except coronary artery disease, congenital heart disease, atrioventricular conduction disturbances, evidence of previously ventricular arrhythmias requiring antiarrhythmic treatment, atrial fi-

Table 1. Preoperative and operative characteristics of patients underwent off-pump coronary artery bypass grafting

Characteristics	Treatment		*P**
	placebo (n=12)	levosimendan (n=12)	
Preoperative data (mean±SD):			
age (years)	61.1±5.3	60.6±5.4	0.747
body surface area (m^2)	2.0±0.1	2.0±0.1	0.563
ejection fraction (%)	58.6±2.4	55.7±4.5	0.196
Medication (n):			
nitrates	5	4	
β-adrenoceptor antagonists	4	4	
calcium channel blockers	2	0	
Coronary occlusion time (min., mean±SD)†	15.4±5.4	16.8±5.7	0.522
No. of grafts (mean±SD)	2.6±0.5	2.7±0.5	0.591

*Mann-Whitney test. SD – standard deviation.
†The sum of single coronary occlusions.

brillation with rapid ventricular response, significant valvular stenosis or regurgitation, or pulmonary hypertension. Patients with myocardial infarction or stroke within 6 months, diabetes mellitus, end-stage of obstructive or restrictive pulmonary disease, severe kidney (serum creatine >115 mmol/L) or hepatic disease (bilirubin 1.5 times above the upper limit of normal), or sepsis were also excluded. Patients taking antiarrhythmic or digoxin therapy and requiring inotropic support before surgery were also excluded from the study. Exclusion criteria during surgery were myocardial ischemia (depression or elevation of the ST-segment for more than 1 mm on 12-lead electrocardiography) and hemodynamic instability (heart rate >100 beats/min, systolic blood pressure <90 mm Hg, or need for cardiac pacing). One patient randomized into the placebo group was subsequently excluded from the investigation and data analysis because he met exclusion criteria during surgery (dopamine administration after induction of anesthesia).

The study complied with the Helsinki Declaration. All patients were informed about the investigation and signed an informed consent form before the surgery.

Anesthesia Procedure

Patients received their cardiac medications on the morning of surgery. Long-acting medications (calcium antagonists and angiotensin converting enzyme inhibitors) were discontinued a day before the beginning of the study. All patients were premedicated with morphine in the dose of 0.1 mg/kg IM (Morphine Merck®, Merck KgaA, Darmstadt, Germany) an hour before surgery. Anesthesia was induced by 0.1 mg/kg IV midazolam (Dormicum®, F. Hoffman-La Roche Ltd., Basel, Switzerland), 5-7 μg/kg IV fentanyl (Fentanyl®, Janssen Pharmaceutica, Beerse, Belgium), and 0.1 mg/kg IV pancuronium-bromide (Pavulon®, N.V. Organon, Oss, the Netherlands). After endotracheal intubation, the lungs were mechanically ventilated by positive pressure (tidal volume of 8 mL/kg and ventilatory frequency of 12/min) (Cato, Dräger, Lübeck, Germany). Tidal volume and respiratory rate were adjusted to maintain acid-base status and arterial CO_2 pressure within physiological limits. Anesthesia was maintained with a nitrous-oxide mixture (60% oxygen and 40% nitrous oxide) and sevoflurane (Sevorane®, Abbott Laboratories S.A., Abbott Park, IL, USA) in doses of 1.0-1.3 minimal alveolar concentration (MAC). Additional doses of pancuronium-bromide (0.1 mg/kg) were administered as required to maintain neuromuscular blockade during surgery.

Hemodynamic Monitoring

American Society of Anesthesiologists (ASA) standard monitors were applied on the admission to the operating room. In the operating room, an arterial catheter (Arrow International, Reading, PA, USA) was inserted into the left radial artery at the angle of 35% to the plane of the wrist, to measure direct arterial blood pressure. Seldinger's technique (16) was used for the central venous catheter placing and for the placing of a 5-lumen, 7.5 French pulmonary artery catheter (PAC) (Arrow International) into the right internal jugular vein. PAC insertion through the jugular vein across the heart into a pulmonary artery branch controlled by the monitor (Hewlett Packard Viridia CMS; Böblingen, Germany). PAC was fixed after being placed into the pulmonary capillary wedge position, usually 55-60 cm from the internal jugular vein puncture site. Central venous, radial and pulmonary arterial pressure transducers (Peter von Berg, Kirschseeon, Germany) were zeroed at the level of the left atrium. Electrocardiographic leads II and V_5, heart rate, central venous, radial, and pulmonary artery pressure curves and values were monitored on the same monitor in the same way through the study.

Bolus thermodilution with the PAC is presently the method for measuring cardiac output in our clinical setting. By this method, multiple cardiac output measurements can be obtained at intervals by using an inert indicator. A 10mL bolus of 5% glucose was injected into the right atrium as the indicator of the room temperature; the following temperature changes were detected by the thermistor on the top of pulmonary catheter. During the patient's exhalation, an indicator was injected over 4 seconds throughout the proximal port of the catheter. The thermodilution curve was monitored on the thermodilution monitor (Cardiac Output Computer; Arrow International). Five repeated measurements were done. The cardiac output mean value was calculated from the three of five measurements not differing reciprocally by more than 10%. Other hemodynamic parameters, such as mean arterial pressure, central venous pres-

sure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, were followed up.

Immediately after the induction of anesthesia, the transesophageal echo with 5.0 MHz biplane probe of the Ultrasound Scanner (Hitachi EUB-555®; Hitachi Medical Corporation, Tokyo, Japan) was inserted and positioned in the stomach. Superior angulation (flexing the scope) in the 0° image plane yielded the transgastric mid short-axis view. At this level, we determined both the left ventricular end-systolic dimension and left ventricular end-diastolic dimension. By recording the left ventricle cross-sectional view, we measured the percent fractional shortening and calculated the EF by Teichholz's method.

Study Design

The patients were randomized into two groups by a single anesthesiologist who drew patients' numbers from a hat on the day before surgery. One group received placebo and the other 12 μg/kg loading dose of levosimendan (Simdax®, Orion Corporation, Espoo, Finland) during a period of 15 minutes. All other investigators were blinded to the randomization. To maintain the randomization blind, each patient received two simultaneous infusions, one active or one placebo. The placebo infusion regimen was visually identical to its respective active counterpart (riboflavinophosphate 0.4 mg, ethanol 100 mg, and 5% glucose yielding a yellow color). Drug infusion started 10 minutes after anesthesia was induced and before surgery via a central vein by an infusion pump Omnifuse Graseby (SIMS Graseby Ltd; Watford, UK). After induction of anesthesia, infusion of 500 mL hydroxyethylstarch 6% solution (HAES-sterile 6% in saline 0.9%, Fresenius Kabi, Bad Homburg, Germany) was administered in all patients to optimize preload.

Heart rate, cardiac index (CI), stroke volume index (SVI), and left ventricular EF were measured before and 10 and 60 minutes after levosimendan administration. The same surgical team performed surgery in all investigated patients.

Statistical Analysis

Numerical data were presented as mean ± standard deviation (SD) or median with interquartile range. Qualitative data were described by frequencies. We used Mann-Whitney test to find differences between the two groups, and Friedman test to compare parameters measured at different time points within each group. Wilcoxon Signed Rank test was applied to find the differences in time-dependent variable pairs between the two groups. For statistical analysis, SAS System for Windows Release 6.12 software (SAS Institute Inc., Cary, NC, USA) was used. Changes were considered statistically significant at $P<0.05$.

Results

Patients in both groups had similar demographic characteristics, preoperative left ventricular EF, medications, and operative data (Table 1). No differences in the heart rate ($P=0.323$) were observed between the baseline measurements (84.0 ± 5.7 beats/min), 10 minutes (83.6 ± 4.0 beats/min), and 60 minutes (82.7 ± 5.1 beats/min) after placebo administration. No differences in the heart rate ($P=0.098$) were found between baseline measurements (83.5 ± 5.3 beats/min), 10 minutes (85.2±4.2 beats/min), and 60 minutes (86.2±4.9 beats/min) after levosimendan administration. The heart rate did not differ between the groups at baseline ($P=0.534$), 10 minutes ($P=0.487$), or 60 minutes ($P=0.078$) after the administration of placebo or levosimendan.

No differences were observed between the groups in the baseline values of hemodynamic parameters (cardiac index and stroke volume index) and left ventricular EF (Table 2).

There were no differences in cardiac index within the placebo group at different time

Table 2. Hemodynamic parameters (median, interquartile range) of myocardial contractility after 15-minute infusion of either placebo) or 12 μg/kg levosimendan in off-pump coronary artery bypass

Hemodynamic parameters	Treatment		*P**
	placebo (n=12)	levosimendan (n=12)	
Cardiac index (L/min/m²):			
baseline	2.21 (1.26)	2.18 (0.32)	0.949
10 min	2.25 (0.98)	2.90 (0.98)	0.035
60 min	2.16 (0.20)	2.84 (1.56)	0.002
P†	0.368	0.004	
Stroke volume index (mL/beat/m²):			
baseline	29.5 (5.5)	30.3 (7.0)	0.201
10 min	29.1 (10.0)	41.2 (18.3)	0.035
60 min	28.3 (10.0)	34.8 (12.5)	0.055
P†	0.368	0.028	
Left ventricular ejection fraction (%):			
baseline	60.0 (9.0)	57.0 (10.0)	0.898
10 min	56.0 (7.0)	71.0 (13.0)	0.004
60 min	57.0 (7.0)	67.0 (13.0)	0.015
P†	0.021	0.002	

*Mann-Whitney test.
†Friedman test.

points. In the levosimendan group, cardiac index was significantly higher 10 and 60 minutes ($P=0.018$ for all) after the administration of the drug than at the baseline measurement.

Similar alterations in stroke volume index were observed within the placebo group. Compared with baseline measurement, stroke volume index was significantly higher 10 ($P=0.018$), but not 60 minutes ($P=0.063$) after the administration of levosimendan.

Significant decrease in the left ventricular EF was obtained after the administration of placebo ($P=0.021$). In comparison with the baseline measurement, the left ventricular EF was significantly lower 10 minutes ($P=0.042$) after the administration of placebo. In contrast to these findings, the left ventricular EF significantly increased in patients who received levosimendan ($P=0.002$). When compared with baseline values, this parameter was significantly higher 10 and 60 minutes ($P=0.018$ for all) after the administration of levosimendan (Table 2).

Discussion

Levosimendan dose that we used had a prolonged effect on the left ventricular systolic function during OPCABG. Unlike Nijhawan et al (13), we did not consider continuous infusion of the drug necessary because the cardiac index was still increased 60 minutes after the application of the loading dose of levosimendan. No increase was noted after the placebo administration. Stroke volume index also increased 10 minutes after administration of levosimendan, whereas it remained unchanged in the placebo group. As some authors previously reported (13,17), lower loading doses of levosimendan (12 μg/kg) do not increase heart frequency. There was no evidence of tachycardia in our patients, with the highest mean value of 86 beats/min. The lack of tachycardia in patients with coronary artery disease decreases the incidence of myocardial ischemia, and on the other hand, guarantees better operation field to surgeon. Estimated increase in cardiac index was only the consequence of a positive effect of levosimendan on the stroke volume index.

In contrast to our results, Lilleberg et al (14) used the high doses of levosimendan, and recorded an increase in the cardiac output as the result of increased stroke volume, but with a consequently increasing heart rate. Because of that, lower loading dose of levosimendan is necessary in patients with coronary artery disease in cardiac surgery. Values of EF, compared with the basic values, increased in the levosimendan group by 14% and 10% after 10 and 60 minutes, respectively. In the placebo group, the both measurements had shown reduced EF.

To test if levosimendan could improve heart function after cardiopulmonary bypass, Nijhawan et al (13) administered continued levosimendan infusion (0.1-0.3 μg/kg/min), after the low and high loading doses, up to 6 hours after the weaning from cardiopulmonary bypass. However, they followed up the hemodynamic effect only by thermodilution and did not use transesophageal ultrasound, as we did. They concluded that levosimendan had a beneficial effect on myocardial function and lowered the afterload following cardiopulmonary bypass.

In the last several years, OPCABG surgery has been used more often, primarily to avoid complications of cardiopulmonary bypass. However, OPCABG procedure can cause a hemodynamic instability due to heart displacement. Additionally, accompanied increasing heart filling pressures could lead to a decrease in cardiac and stroke volume indices.

Presently, there is still no consensus on vasoactive medications use during the OPCABG surgery. Beta-adrenoceptor agonists could impair myocardial function by increased oxygen consumption, and their positive chronotropic effect can make surgeon's job more difficult. As arterial grafts (radial and mammary arteries) allow for better flow than veins grafts, they are increasingly used in surgery (18). In patients who received arterial grafts, alternative use of vasoconstrictors can produce vasospasm and lead to dramatic hemodynamic deterioration (19). Furthermore, vasoconstrictors can additionally decrease cardiac index as they increase afterload (19). The brief period of ischemia during direct coronary occlusion is characterized by reversibly impaired postischemic systolic and diastolic function (20). The mechanism of myocardial stunning is connected directly with decreased calcium sensitivity of myofibrils (21). Because of the unfortunate effects of the previously mentioned vasoconstrictors and beta-adrenoceptor agonists, levosimendan could be an alternative agent during OPCABG. Levosimendan is a calcium sensitizer that enhances the

contractile force of the myocardium by binding to troponin C without increasing intracellular calcium concentration at therapeutic doses (22). It exerts cardioprotective effects, including coronary artery vasodilatation via activation of triphosphate-regulated potassium channels at a dose that enhances myocardial contractility (23). On the other hand, there is still no protocol for use of inotropic medications. In Europe, they are used in 30% to 100% of cardiosurgery procedures (24). Due to potential adverse effects of catecholamine inotropic medications, some authors report a potentially higher risk of complications (24).

The limitations of this study were a small number of patients and specific surgery procedure (cardiopulmonary bypass was not performed). A possible shortcoming of levosimendan usage in cardiosurgery patients could be the fall of blood pressure due to the decrease in the right ventricular filling pressure. The same mechanism, based on the baroreceptors activation, could aggravate reflex tachycardia. However, reflex tachycardia was not registered in our study, because we used a lower dose of levosimendan, which could additionally limit the results of this study. Favorable hemodynamic effect of levosimendan, as shown in our study, could hasten the healing and decrease the patients' length of stay in intensive care units. However, these results have to be interpreted with caution in patients with preoperative left-sided heart failure and hemodynamic criteria for low cardiac output syndrome.

In conclusion, levosimendan offers a promising therapeutic choice for the management of patients with optimal hemodynamic stability. It also enhances left ventricular performance during OPCABG in patients with good preoperative left ventricular function. Further clinical investigations should include patients with low cardiac output syndrome in early postoperative period and those with diastolic myocardial dysfunction, and should provide answers to questions about oxygen balance in the myocardium and potential unfavorable effects of levosimendan on intrapulmonary shunt.

References

1 Sohrabi F, Mispireta LA, Fiocco M, Dibos LA, Buescher PC, Sloane PJ. Effects of off-pump coronary artery bypass grafting on patient outcome. J Investig Med. 2003; 51:27-31.

2 Eldrup N, Rasmussen NH, Yndgaard S, Bigler D, Berthelsen PG. Impact of off-pump coronary artery surgery on myocardial performance and beta-adrenoceptor function. J Cardiothorac Vasc Anesth. 2001;15: 428-32.

3 Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, et al. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. JAMA. 2004;291:1841-9.

4 Al-Ruzzeh S, Ambler G, Asimakopoulos G, Omar RZ, Hasan R, Fabri B, et al. Off-Pump Coronary Artery Bypass (OPCAB) surgery reduces risk-stratified morbidity and mortality: a United Kingdom multi-center comparative analysis of early clinical outcome. Circulation. 2003;108 Suppl 1:1-8.

5 Nierich AP, Diephuis J, Jansen EW, Borst C, Knape JT. Heart displacement during off-pump CABG: how well is it tolerated? Ann Thorac Surg. 2000;70:466-72.

6 Kwak YL, Oh YJ, Jung SM, Yoo KJ, Lee JH, Hong YW. Change in right ventricular function during off-pump coronary artery bypass graft surgery. Eur J Cardiothorac Surg. 2004;25:572-7.

7 Mathison M, Edgerton JR, Horswell JL, Akin JJ, Mack MJ. Analysis of hemodynamic changes during beating heart surgical procedures. Ann Thorac Surg. 2000;70: 1355-60.

8 Sun H, Cjhartier D, Leblanc N, Nattel S. Intracellular calcium changes and tachycardia-induced contractile dysfunction in canine atrial myocytes. Cardiovasc Res. 2001;49:751-61.

9 Kwak YL, Oh YJ, Shinn HK, Yoo KJ, Kim SH, Hong YW. Haemodynamic effects of a milrinone infusion without a bolus in patients undergoing off-pump coronary artery bypass graft surgery. Anaesthesia. 2004;59:324-31.

10 Kim JH, Ham BM, Kim YL, Bahk JH, Ryu HG, Jeon YS, et al. Prophylactic milrinone during OPCAB of posterior vessels: implication in angina patients taking beta-blockers. Eur J Cardiothorac Surg. 2003;24:770-6.

11 Figgit DP, Gillies PS, Goa KL. Levosimendan. Drugs. 2001;61:613-27.

12 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.

13 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 Cardiovas Pharmacol. 1999;34:219-28.

14 Lilleberg J, Nieminen MS, Akkila J, Heikkilä L, Kuitunen A, Lehtonen L, et al. Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J. 1998;19: 660-8.

15 Dupuis JY, Wang F, Nathan H, Lam M, Grimes S, Bourke M. The cardiac anesthesia risk evaluation score. Anesthesiology. 2001;94:194-204.

16 Seldinger SI. Catheter replacement of the needle in percutaneous arteriography. Acta Radiol. 1953;39:368.

17 Barisin S, Husedzinovic I, Sonicki Z, Bradic N, Barisin A, Tonkovic D. Levosimendan in off-pump coronary artery bypass: a four-times masked controlled study. J Cardiovasc Pharmacol. 2004;44:703-8.

18 Zacharias A, Habib RH, Schvann TA, Riordan CJ, Durham SJ, Shah A. Improved survival with radial artery versus vein conduits in coronary bypass surgery with left internal thoracic artery to left anterior descending artery grafting. Circulation. 2004;109:1489-96.

19 Kerendi F, Halkos ME, Corvera JS, Kin H, Zhao ZQ, Mosunjac M, et al. Inhibition of myosin light chain kinase provides prolonged attenuation of radial artery vasospasm. Eur J Cardiothorac Surg. 2004;26:1149-55.

20 Royse CF, Royse AG, Wong CT. Assessment of left ventricular function during off-pump coronary artery bypass surgery. Ann Thorac Cardiovasc Surg. 2003;9:371-7.

21 Eberli FR. Stunned myocardium-an unfinished puzzle. Cardiovasc Res. 2004;63:189-91.

22 Haikala H, Nissinen E, Etemadzadeh E, Levijoki J, Linden IB. Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol. 1995;25:794-801

23 Lehmann A, Boldt J, Kirchner J. The role of Ca++-sensitizers for the treatment of heart failure. Curr Opin Crit Care. 2003;9:337-44.

24 Heismayr MJ. Cardiac anesthesia and intensive care: the forgotten connection. In: Proceedings of 18th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologist; 2003 May 25-28; Prague (Czech Republic): Publishing House Galén Ltd; 2003. p. 53-6.

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