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Research Article

Levosimendan's effect on coronary artery grafts blood flow in patients with left ventricular dysfunction, assessment by transit time flow meter

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KEYWORDS

Coronary graft flow;
Levosimendan;
Transit time flow meter

Abstract *Objectives:* Levosimendan improves the function of stunned myocardium and cardiac performance in heart failure without significantly increasing myocardial oxygen consumption. We evaluated the effects of levosimendan on hemodynamics and coronary grafts blood flow (CBF) in patients with left ventricular dysfunction undergoing pump coronary artery bypass grafts (CABG) surgery using transit time flow meter (TTFM).

Methods: Twenty patients with stable angina and left ventricular ejection fraction 30–50% scheduled for elective CABG surgery were randomized to receive levosimendan (0.1 mg/kg/min) or placebo, started immediately after induction of anesthesia and continued for 24 h in ICU. Coronary bypass grafts flow was measured 30 min after termination of cardiopulmonary bypass (CPB). Flow curve pattern, mean graft flow, and pulsatile index (PI) were measured and analyzed. Hemodynamics was collected serially at five time points.

Results: Mean flow in all grafts was significantly higher in the Levosimendan group in comparison to control group ($p < 0.05$). When we compared mean flow between different types of grafts in Levosimendan group, we found that venous sequential grafts had higher flow than non-sequential graft ($p < 0.001$) and arterial grafts ($p = 0.005$). Also saphenous vein grafts (SVG) had higher flow in comparison to left internal mammary artery (LIMA) grafts ($p = 0.004$). As regard PI, it was also

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more significant in the Levosimendan group for all grafts ($p < 0.001$) in comparison to control group. Intragroup comparison of PI values between different types of grafts in Levosimendan group showed more significant PI values in sequential grafts ($p = 0.002$) in relation to SVG, and also it was more significant in comparison to LIMA grafts ($p = 0.0027$).

Conclusions: Levosimendan significantly increased the flow in arterial and vein grafts after CPB, and improved hemodynamics compared with placebo.

1. Introduction

Levosimendan is a new calcium-sensitizing agent that has been developed for the treatment of decompensated heart failure. Levosimendan enhances myofilaments contractility mainly via its calcium-sensitizing actions by binding to cardiac troponin C in a calcium-dependent manner and induces peripheral and coronary vasodilation by opening the adenosine triphosphate-sensitive potassium channels [1,2].

Administration of levosimendan in patients undergoing elective cardiac surgery significantly increased cardiac output, heart rate and stroke volume without significantly increasing myocardial oxygen consumption or changing the utilization of myocardial substrates. A similar 'neutral' effect of levosimendan on myocardial energetics has also been demonstrated in healthy volunteers, whereas adrenergic agonists such as dobutamine increased oxygen consumption in addition to contractility [3]. Moreover, a recent study demonstrated that levosimendan is safe in patients with acute coronary syndrome who underwent a percutaneous coronary intervention (PCI), and improves the function of stunned myocardium [4].

Several methods have been used to assess graft patency intraoperatively, including manual palpation of the graft, direct probing of the anastomosis, graft patency testing with syringe, and ultrasound-based flow meters such as Doppler and transit time flow measurement (TTFM) and intraoperative angiography. Among those methods, TTFM has been used with increasing frequency because it is considered to be a convenient and reliable way to document graft patency and subsequent correction of graft related problems intraoperatively [5,6].

The aim of this study was to detect the effects of Levosimendan on coronary graft flow after cardiopulmonary bypass, by using transit time flow meter in patients undergoing elective CABG surgery.

2. Patients and methods

2.1. Patient population and study design

This prospective, randomized trial was conducted at The Chest Diseases Hospital, Kuwait over a period of 6 months starting from January 2009 to June 2009. The ethics and review board at the hospital approved the study protocol, and all patients gave written informed consent. Twenty patients were included after they satisfied the following criterion: isolated non-urgent on-pump CABG surgery with left ventricular ejection fraction 30–50%. Exclusion criteria were; valvular heart disease, marked mechanical obstructions affecting ventricular filling or outflow or both, evolving myocardial infarction (< 7 days), preoperative hemodynamic instability (severe hypotension or serious arrhythmias), severe renal impairment (plasma creatinine > 2.5 mg/dL) and severe hepatic disease (liver enzymes > 2 times the upper limit of normal).

The patients were randomized by sealed envelopes to the Levosimendan group (10 patients) or the placebo group (10 patients). Nurses who did not participate in the study prepared the drugs in 50 ml syringes according to the table of randomization. Drugs administration and data collection were performed in a double-blind fashion in which neither the patients nor the medical team were aware about the injected drugs. The treatment group received levosimendan (Simdax; Orion Corp, Espoo, Finland), (5 ml of the drug 2.5 mg/ml diluted in 500 ml 5% dextrose solution → 0.025 mg/ml solution for infusion) at a dose of 0.1 mg/kg/min started immediately after the induction of anesthesia and continued for 24 h in ICU. According to the standard practice in the hospital, no bolus dose of the drug was administered because of concern for severe hypotension associated with the bolus dose of the drug. The control patients received a placebo (thiamin-colored 5% glucose) infusion of equivalent volume over the same time interval.

2.2. Methods

2.2.1. Anesthesia and surgical techniques

Two hours before surgery, an equipotent dose of oral metoprolol was given for the patients who were on preoperative β-blockers. Thirty minutes before the induction of anesthesia, the patients were premedicated with intramuscular morphine 0.1 mg/kg. After reaching the operating theater, the standard monitors were attached to the patients. A continuous cardiac output pulmonary artery catheter (Edwards Lifesciences, Irvine, CA), inserted after the induction of anesthesia, also a urinary bladder catheter with a temperature probe was inserted for temperature and urine-output monitoring. All patients were induced with midazolam (0.05 mg/kg), sufentanil (0.5 μg/kg), propofol (1.0 mg/kg), and an intubating dose of rocuronium. Anesthesia was maintained with air/O_2, sevoflurane, and sufentanil (infusion 0.5 μg/kg/h). Mechanical ventilation was maintained with a tidal volume of 6–8 ml/kg and frequency of 10–12 breaths/min. During CPB, anesthesia was maintained using propofol infusion at a rate of 3 mg/kg/h.

Heparin sulfate 4 mg/kg was administered prior to CPB and supplemented as needed to maintain an activated clotting time (ACT) of at least 400 s. CPB was conducted with a roller pump (Stockert S3, Sorin Group, Deutschland, München, Germany) using membrane oxygenator (Medtronic, USA) and 40-μ arterial line filter with non-pulsatile perfusion (at a flow rate of 2.4 l/min/m^2). Saint Thomas cardioplegia solution (potassium 20 mmol/l) was delivered through the antegrade and retrograde routes (diluted with blood 1:4) every 20 min. Systemic temperature was allowed to drift to 35 °C.

During rewarming, pulmonary capillary wedge pressure (PCWP) was kept between 13 and 16 mm Hg using IV fluids. Dobutamine was administered in both groups if the cardiac index (CI) fell below 2.0 l/min/m^2 with PCWP above 15 mm Hg and a mean arterial blood pressure (MAP) below 65 mm Hg. Dobutamine was initiated and increased until haemodynamic targets were achieved (CI 2.3–2.5 l/min/m^2). When a patient had an MAP $\leqslant$60 mm Hg and systemic vascular resistance (SVR) $\leqslant$ 600 dynes/s/cm^5, a Norepinephrine infusion was also started. The treatment goal was to achieve a MAP $\geqslant$70 mm Hg, CI $\geqslant$2.4 l/min/m^2, PCWP $<$18 mm Hg, and SVR $<$1200 dynes/s/cm^5.

After separation from CPB and removal of the aortic cannula, heparin activity was neutralized with protamine sulfate. Upon arrival in the ICU, the patient's condition was evaluated and kept sedated for 2 h with propofol 0.5 mg/kg/h plus intermittent boluses of morphine (2–4 mg every 30 min as needed) until hemodynamic variables and temperature were stable. Weaning from mechanical ventilation and tracheal extubation followed a standard protocol.

2.2.2. Intraoperative measurement of grafts flow by TTFM

Graft flow measurements were performed 30 min after the termination of CPB and after the reversal of heparin. MAP was maintained between 80 and 90 mm Hg during the flow measurement. The same transit time flowmeter (MediStim VQ-1101, MediStim ASA, Oslo, Norway) was calibrated and used in all patients. The TTFM probe was perfectly fitted around the graft by using different probe sizes to avoid distortion or compression of the graft. The following variables can be obtained and analyzed: (1) flow curve pattern; (2) mean graft flow; (3) pulsatility index (PI) ([maximal flow − minimal flow]/mean flow); (4) percentage of backward flow (% BF) (or it is called insufficiency ratio – IR), as the amount of flow through the graft directed backward across the anastomotic site and (5) diastolic filling percentage (DF%) (Fig. 1) [7].

To correctly address TTFM findings, flow curves, pulsatile index (PI) and mean flow values should be evaluated simultaneously. The curves are coupled with the ECG tracing to correctly differentiate systolic from the diastolic flow. In a patent coronary graft, blood flows mainly during diastole with minimal systolic peaks taking place during the isovolumetric ventricular contraction (QRS complex) [8]. Mean flow is largely dependent on the quality of the native coronary artery, and low mean flow can be expected in fully patent anastomoses whenever the target territory has a poor runoff [9]. Mean flows of less than 15 ml/min is considered to be questionable. The PI is a good indicator of the flow pattern and, consequently, of the quality of the anastomosis. The pulsatility index (PI) value should ideally be between 1 and 5. The possibility of a technical error in the anastomosis increases for higher PI values $>$ 5 [10], DF $<$ 50% and/or insufficiency ratio (% BF values) greater than 3% [8].

2.2.3. Data collection

Heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance index (PVRI) and mixed venous oxygen saturation (SvO_2) were collected after the induction of anesthesia and before the start of study drugs (base line) (T0), 15 min post CPB (T1), at the end of the operation (T2), 6 h after ICU admission (T3) and 24 h after ICU admission(T4). Troponin I and arterial lactate were collected at base line after the induction of anesthesia, on ICU admission, 6 and 24 h from ICU admission. Duration of tracheal intubation, ICU stay and mortality among the study patients were documented.

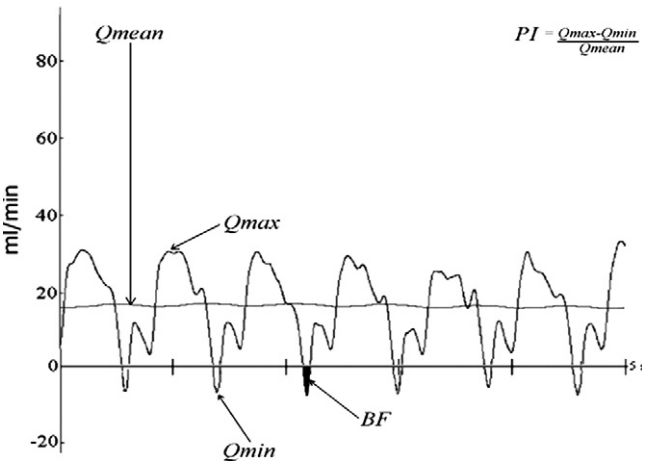


Figure 1 The trace shows a normal curve with its parameters. Q_{mean}, Mean flow; Q_{max}, maximum flow; Q_{min}, minimum flow; PI, pulsatility index; BF, backward flow [7].

2.2.4. Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (±SD), 95% CI of the mean, median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney *U* test for independent samples when comparing two groups and Kruskal Wallis test with Conover Inman posthoc test in comparing more than two groups. Within group comparison of quantitative variables was done using Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than five. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Sample size calculation was done using mean flow as it was considered the primary outcome of our study with one control(s) per experimental subject. In a previous study, the response within each subject group was normally distributed with a standard deviation 10. If the true difference in the experimental and control means is 20, we will need to study around 10 experimental subjects and 10 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with 80% power. Type I error probability associated with this test of this null hypothesis is 0.05. Calculations were done using PS Power and Sample Size Calculations software, version 2.1.30 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

3. Results

Twenty patients were enrolled and completed the study. There were no statistically significant differences in demographic data, preoperative ejection fraction and risk factors among the two studied groups (Table 1). Operative data were similar among the two groups. Types of grafts (LIMA, SVG or Radial artery) and distribution of anastomosis (Lt System, right system or sequential) were also similar between the two studied groups. LIMA grafts were only anastomosed to LAD (Table 2).

The changes in **hemodynamic parameters** are shown in Table 3. At baseline, there were no differences between Levosimendan and control group in hemodynamic variables. In contrast, post CPB and during ICU course (T1–T4), the recorded HR showed a significant increase in the two groups in comparison to base line but it was significantly higher in Levosimendan group ($p < 0.001$). MAP showed a significant increase in both groups in relation to baseline to reach the maximal levels at 24 h after ICU admission and there was a significant difference between the two groups ($p < 0.005$). Fifteen minutes post CPB (T1) and at the end of surgery (T2), SVRI and PVRI, dropped significantly in both groups in comparison to baseline ($p < 0.005$), but Levosimendan group was significantly lower than control groups ($p < 0.001$), then started to increase during ICU course in the two groups but still below baseline. Cardiac index showed a significant increase in both groups post CPB with marked improvement in Levosimendan group, which started 15 min post CPB then continued during ICU course. The increases were significantly higher in the Levosimendan group than in the control group ($p < 0.001$). SVO2 values showed significant improvement in both groups post CPB and during ICU course ($p < 0.05$), with much more increase in Levosimendan group only at T1 and T2 ($p = 0.003$ and 0.001, respectively).

The number of patients who required norepinephrine during the weaning of CPB to maintain perfusion pressure was significantly greater in the levosimendan group (five patients) than in the control group (two patients) ($p < 0.05$). Dobutamine was needed for five patients in the placebo group and for four patients in the levosimendan group.

Table 1 Demographic data and risk factors.

	Levosimendan ($n = 10$)	Placebo ($n = 10$)	p-value*
Age (year)	60 ± 10	58 ± 8	0.627
Sex (M/F)	8/2	7/3	1.000
BSA	1.92 ± 0.16	1.89 ± 0.10	0.621
Ejection fraction	36 ± 2	38 ± 3	0.096
Risk factors (*no of patients*)			
Diabetes	9	7	0.576
HTN	7	5	0.648
COPD	3	1	0.576
Medication (*no of patients*)			
ACE inhibitors	5	4	1.000
β blockers	10	10	1.00

Data are presented as mean ± SD and ratio for sex.
BSA, body surface area; HTN, hypertension; COPD, chronic obstructive pulmonary disease.
* p-value levo. vs placebo.

Table 2 Operative data.

Variable	Levosimendan ($n = 10$)	Placebo ($n = 10$)	p-value*
Aortic cross-clamp (min)	59 ± 11.8	67 ± 12.5	0.158
Cardiopulmonary bypass (min)	103 ± 25	112 ± 22	0.404
Grafts/patient	2.8 ± 0.5	2.7 ± 0.7	0.717
Number of grafts-total (*n*)	26	24	
LIMA	10	9	0.825
Saphenous vein grafts	16	15	0.794
Sequential grafts	2	3	0.925
Total distal anastomosis (*n*)	28	27	
LAD	10	10	0.858
Diagonal	5	4	0.952
Cx system	7	8	0.934
RCA system	6	5	0.946

Data are presented as mean ± SD.
LAD, left anterior descending artery; Cx system, circumflex system; RCA system, right coronary artery system; LIMA, left internal mammary artery.
* p-value, levo. vs. placebo.

Graft flow values of TTFM are shown in Table 4, Figs. 2 and 3. In both groups, flow curve patterns were mainly during diastole with minimal systolic peaks. In comparison to control group, the mean flow in all grafts was significantly higher in the Levosimendan group 30 min after CPB ($p < 0.05$). When we compared mean flow between different types of grafts in the same group, in the Levosimendan group, we found that venous sequential grafts had higher flow than non-sequential graft ($p < 0.001$) and arterial grafts ($p = 0.005$). Also the SVG had higher flow in comparison to LIMA grafts ($p = 0.004$).

As regard PI, it was statistically significant (lower values) in the Levosimendan group when compared to the control group in all grafts ($p < 0.001$). When we compared PI values between different types of grafts in the same group, we found that in the Levosimendan group, there were no statistically significant differences ($p = 0.8704$) between LIMA and SVG but when we compared PI between sequential grafts and SVG, it was more significant in sequential grafts ($p = 0.002$) and also it was more significant in comparison to LIMA grafts ($p = 0.0027$).

Two grafts, one graft in levosimendan group and one in placebo group, in whom unsatisfactory TTFM findings were detected the mean flow & PI values were 14 ml/min & 4.2 and 14 ml/min & 5.0, respectively. Revision of the anastomosis was performed and the operation was ended when a good flow was within satisfactory ranges (Figs. 4 and 5).

Troponin-I and arterial lactate release were detected in both groups post-operatively with significantly higher values ($p < 0.001$) in control group (Table 5). The time for extubation in ICU was insignificant among the two studied groups and the postoperative course of the patients was uneventful.

4. Discussion

In the present study, we investigated the effect of levosimendan infusion on coronary grafts blood flow (CBF) in ischemic patients with LV dysfunction who underwent CABG surgery and we found a marked improvement in hemodynamic parameters and Coronary blood flow; greater in both arterial and saphe-

Table 3 Hemodynamic and oxygenation variables.

Each group (10 patients)	Baseline (T0)	15 min post CPB (T1)	End of surgery (T2)	ICU 6 h (T3)	ICU 24 h (T4)
HR (beat/min)					
Levosimendan	62 ± 2.2	85 ± 2.4*	93 ± 2.1*,**	94 ± 1.5*,**	91 ± 1.4*,**
Placebo	63 ± 2.1	81 ± 1.8*	82 ± 1.3*	80 ± 2*	82 ± 1.2*
MAP (mm Hg)					
Levosimendan	63 ± 2.5	82 ± 1.2*,**	85 ± 2.2*,**	92 ± 1.2*,**	93 ± 1.5*,**
Placebo	63 ± 2.2	76 ± 2.2*	82 ± 1.2*	83 ± 1.5*	81 ± 2*
PCWP (mm Hg)					
Levosimendan	17 ± 1.5	15 ± 1.4	13 ± 1.5*	15 ± 1.7	14 ± 1.4
Placebo	16 ± 1.4	16 ± 1.6	13 ± 1.1*	14 ± 1.0	15 ± 1.4
CVP (mm Hg)					
Levosimendan	7 ± 2	11 ± 3	12 ± 1	9 ± 2	10 ± 3
Placebo	8 ± 1	12 ± 4	10 ± 2	9 ± 3	8 ± 4
SVRI (dyne/s/cm^5/m^2)					
Levosimendan	1859 ± 31.4	1027 ± 13.8*,**	1169 ± 11.9*,**	1250 ± 10.8*,**	1366 ± 8.8*,**
Placebo	1870 ± 6.5	1221 ± 7.5*	1281 ± 5.2*	1459 ± 9.0*	1638 ± 6.9*
PVRI (dynes/s/cm^5/m^2)					
Levosimendan	262 ± 10.3	95 ± 5.8*,**	125 ± 7.0*,**	183 ± 7.1*,**	245 ± 11.9**
Placebo	273 ± 5.8	175 ± 4.5*	210 ± 4.0*	193 ± 4.9*	223 ± 4.7*
CI (L/min/m^2)					
Levosimendan	1.8 ± 0.2	3.8 ± 0.4*,**	3.4 ± 0.2*,**	3.7 ± 0.2*,**	2.7 ± 0.2*,**
Placebo	1.8 ± 0.3	2.7 ± 0.2*	2.6 ± 0.2*	2.4 ± 0.17*	2.5 ± 0.18*
SVO2 (%)					
Levosimendan	64 ± 4. 4	74 ± 3.9*,**	77 ± 3.0*,**	71 ± 2.4*	75 ± 3.1*
Placebo	64 ± 4.5	68 ± 2.5	71 ± 3.2*	71 ± 4.4*	74 ± 2.6*

Data are presented as mean ± SD.
HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; SvO_2, mixed venous oxygen saturation; PVRI, pulmonary vascular resistance index; CI, cardiac index.
* $p < 0.05$ vs. baseline.
** $p < 0.05$ levo. vs. placebo.

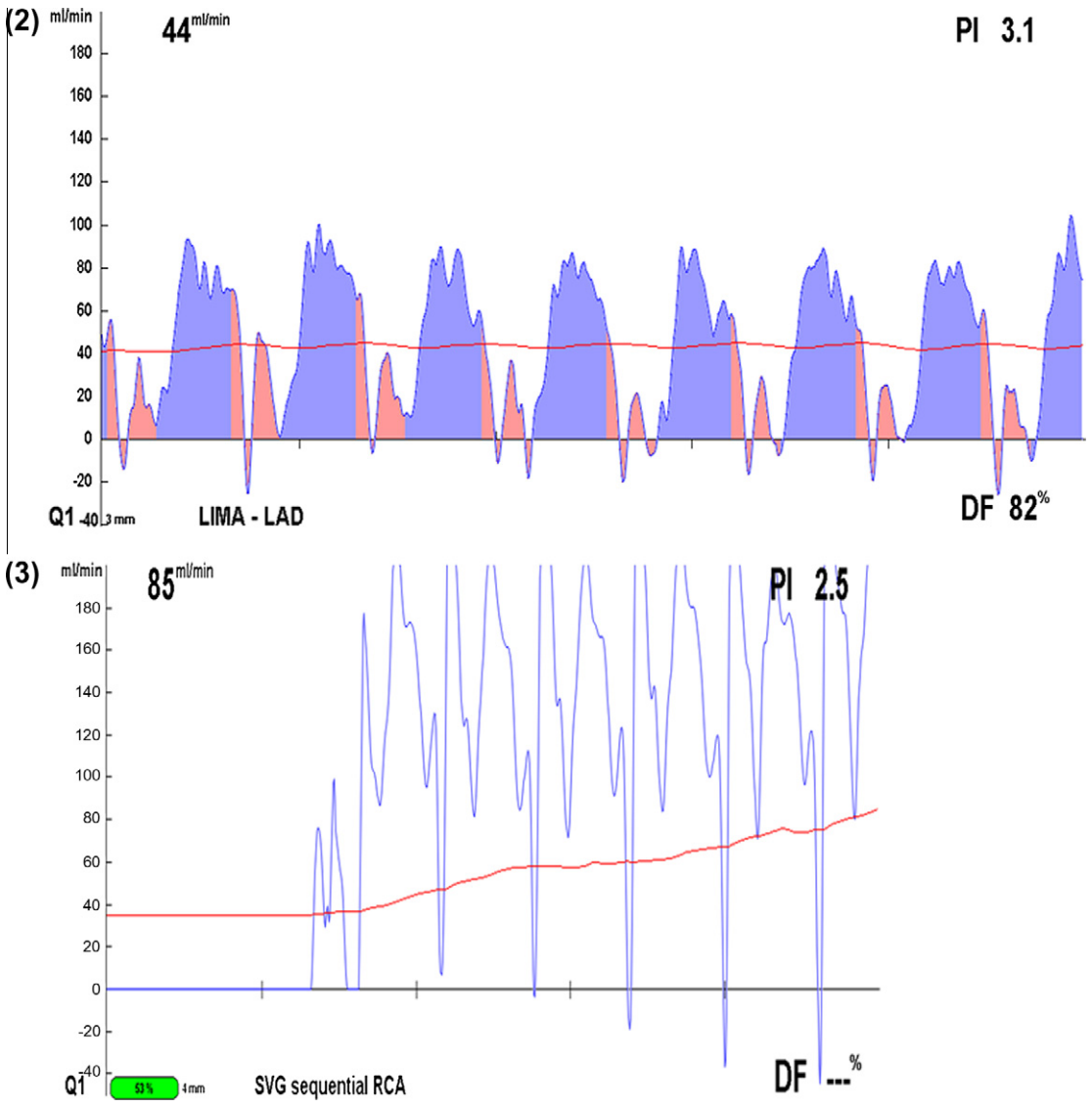
Table 4 Comparison of the TTFM values between the two groups.

	Mean flow	*p*-value	95% CI		P I	*p*-value	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
LIMA–LAD								
Levo	50.15 ± 13.5*	0.016	37.6	62.7	2.4 ± 0.27*	<0.001	2.2	2.6
Placebo	34.7 ± 12.3		23.1	46.4	4.1 ± 0.37		4.0	4.5
SVG-diagonal								
Levo	55.29 ± 12.4*	0.024	43.5	67.0	3.1 ± 0.17*	<0.001	3.0	3.3
Placebo	40.7 ± 14.0		27.9	53.6	4.2 ± 0.2		4.0	4.4
SVG–Cx system								
Levo	56.7 ± 13.4*	0.003	44.4	69.2	2.1 ± 0.2*	<0.001	2.0	2.3
Placebo	36.6 ± 12.5		24.8	48.5	2.7 ± 0.3		2.5	3.0
SVG–RCA system								
Levo	56.5 ± 12.6*	0.004	44.7	68.2	2.2 ± 0.4*	<0.001	2.2	2.7
Placebo	38.8 ± 11.4		27.8	49.9	3.9 ± 0.3		4.0	4.5
Sequential								
Levo	77.6 ± 13.3*	0.016	65.3	90.1	1.8 ± 0.2*	<0.001	1.6	2.0
Placebo	60.7 ± 15.2		47.1	74.4	2.4 ± 0.4		2.17	2.8

Data are presented as mean ± SD.
LIMA–LAD, left internal mammary artery–left anterior descending artery; SVG-diagonal, Savenous vein graft-diagonal; Cx system, circumflex system, RCA system, right coronary artery system.
* *p*-value, levo. vs. placebo group.

nous vein grafts as compared with placebo. In the Levosimendan group, there was a tendency towards higher flow in sequential venous grafts than venous non-sequential and arterial grafts. To our knowledge, no previous study examined the effect of Levosimendan on coronary grafts flow assessed by TTFM.

Changes in graft flow may be due to a direct drug effect on the conduit, coronary vasculature, or a mixture of causes.



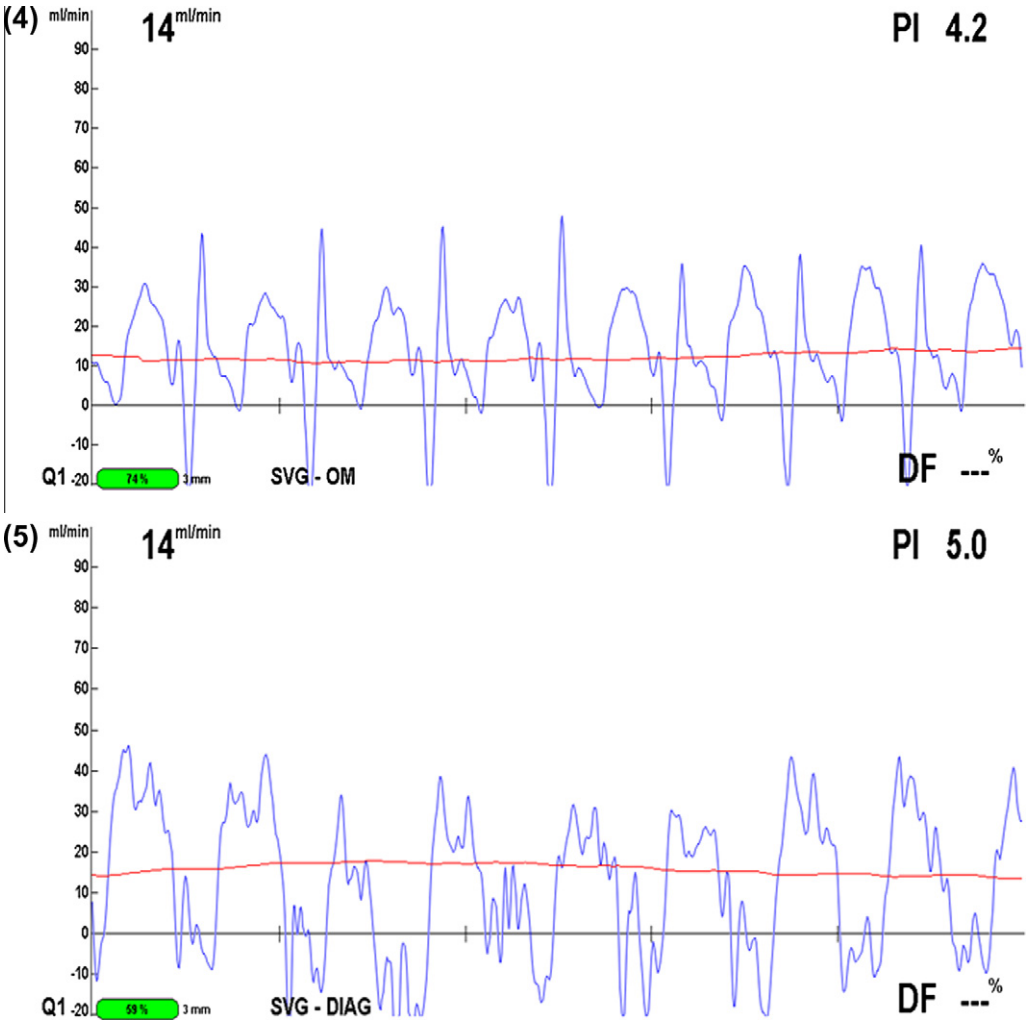
Figures 2 and 3 Normal TTFM values in LIMA–LAD and SVG sequential in Levosimendan group.

Hemodynamic factors, such as blood pressure, HR, and LV function also influence the graft flow. Other factors include the surgical technique and competitive flow through native vessels [11]. So, coronary flow is considered complex and dependent on a large number of dynamic and non-dynamic factors. Graft flow in our study most probably related to changes in hemodynamics and coronary vascular resistance. CI was significantly higher in the Levosimendan group, indicating a better cardiac output possibly because of reduced systemic vascular resistance and increased HR. These findings were coinciding with the study of Lilleberg et al. [2] who documented a significant improvement of CBF and systemic hemodynamics in 23 patients randomized to placebo or two different doses of levosimendan after CABG surgery. Also previous studies [12–15] had demonstrated a vasorelaxant effect of levosimendan on smooth muscle tone of epicardial coronary artery preparations obtained from porcine and human donor hearts.

All venous grafts in our study are manually dilated before being anastomosed, so the effect of Levosimendan on flow in SVGs cannot be explained only by graft dilation. It could be dilation in the native peripheral coronary vessels. A recent study by Maslow et al. [16] comparing vasoactive agents on flow during peripheral vascular surgery suggests that factors affecting SVG flow are not just simply related to systemic hemodynamics. The usual technique of preparing saphenous vein grafts, as used in our study, is known to damage all layers of the vessel wall and may influence its normal reactivity [17]. A recent work by Tsui et al. [18] and Souza et al. [19] designed to preserve integrity of vessel wall called "no-touch" harvesting technique has been described. The long-term patency rate was significantly higher compared with conventionally treated vein grafts.

An electrophysiological studies by Yokoshiki and his colleagues [20] found that Levosimendan activates the glibenclamide-sensitive K + channel in rat arterial myocytes, suggesting that the vasodilator effects of Levosimendan are mediated through opening of the ATP sensitive potassium channel in vascular smooth muscle cells.

In the study by Lilleberg et al. [2] Levosimendan decreased systemic and pulmonary vascular resistance and increased cor-



Figures 4 and 5 Unsatisfactory TTFM findings in patients with SVG-OM and SVG-diagonal.

Table 5 Biochemical profiles.

Each group = 10 patients	Baseline	On ICU admission	ICU 6 h	ICU 24 h
Troponin-I (ng/ml)				
Levosimendan	0.13 ± 0.02	2.3 ± 0.14*	2.5 ± 0.14*	3.1 ± 0.16*
Placebo	0.12 ± 0.01	2.5 ± 0.19*,**	5.2 ± 0.24*,**	7.6 ± 0.27*,**
Lactate (mmol/l)				
Levosimendan	0.72 ± 0.2	1.6 ± 0.14*	1.8 ± 0.19*	2.2 ± 0.17*
Placebo	0.73 ± 0.2	1.8 ± 0.19*,**	2.5 ± 0.16*,**	3.1 ± 0.2*,**

Data are presented as mean ± SD.
* $p < 0.005$ vs. baseline.
** $p < 0.001$ levo. vs. placebo.

onary sinus blood flow significantly. On the other hand, myocardial oxygen consumption or substrate extractions did not change statistically significantly. In our study, troponin-I and lactate releases occurred in either of the groups but it was significantly higher in control group. These findings may indicate that myocardial ischemia and impaired tissue perfusion were mild in Levosimendan group in comparison to placebo group.

The efficacy of Levosimendan in myocardial ischemia was evaluated by previous studies on animal models of global and regional ischemia [21] or in patients with acute myocardial infarction (AMI) [22]. In the study by Moiseyev et al. [23], which randomized 504 patients with LV failure complicating an AMI, patients treated by Levosimendan showed lower risk of death and worsening heart failure than patients receiving placebo. In the study by Sonntag and his colleagues [24], to investigate the effect of levosimendan on stunned myocardium, they compared the effects of levosimendan to placebo on LV function in 24 patients with acute coronary syndrome after a

coronary angioplasty. They recorded LV pressures and volumes 10 min after angioplasty and 20 min after drug administration. A leftward and/or upward shift of the systolic part of the pressure–volume loop was observed, indicating improved systolic function.

Végh et al. [25] have shown in anaesthetized dogs, after experimental acute heart failure induced by ligation of the LAD and critical constriction of the left circumflex artery, that levosimendan increased coronary blood flow and myocardial contractility.

In our study, we found a significant improvement of CI and CBF in patients with moderate LV dysfunction who underwent CABG surgery. These findings were in agreement with the study of Slawsky and his colleagues [26], on hemodynamics and clinical effects of levosimendan in patients with severe heart failure. They found that, levosimendan caused dose-dependent decreases in PCWP, right atrial, and mean arterial pressures and a concomitant increase in CI.

Many studies [7,8] recommended the wide use of TTFM intraoperatively to detect graft patency, because they considered it noninvasive, easy to handle and represent the real flow within the graft. However, the same studies [7,8], documented the potential factors that could affect TTFM values like hemodynamic changes, distal coronary resistance, and graft diameter. In our study we tried to maintain MAP between 80 and 90 mm Hg during the flow measurement. Practically, we cannot rely on mean graft flow as the only measure to diagnose intraoperative poor graft anastomoses. In the study by Jaber et al. [27] demonstrated that mean graft flow did not decrease significantly until graft stenosis was greater than 75%. The pulsatility index value is considered another good indicator of graft quality. The lower limit value of the pulsatility index to confirm successful graft patency has been suggested to be less than five [28]. Gabriele and his colleagues [7], discussed the main obstacle for wider use of TTF technology until now, and they found that no clear-cut values for TTFM measurements and lack of objective parameters to predict graft failure.

There is one limitation in our study, the use of other vasoactive drugs (dobutamine and norepinephrine) was an additional confounding factor, therefore, interaction between levosimendan and norepinephrine is possible. Thereby, the overall effects on different vascular beds may be unpredictable.

In conclusion, Levosimendan, given intravenously during CABG surgery in patients with LV dysfunction, significantly improved hemodynamics and coronary blood flow compared with placebo.

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