# A comparative Study between Levosimendan and Dobutamine for Treatment of Low Cardiac Output Syndrome after cardiac surgery

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# Aim of the work

The aim of the present work is to compare the short-term hemodynamic effects of levosimendan and dobutamine in a group of patients with post-operative low cardiac output after surgery involving ECC.

The secondary aims are to assess the efficacy and safety of both treatments, expressed as the number of patients showing a normalized cardiac index and the number of subjects which we cannot continue the treatment because of continued low cardiac output or the appearance of adverse effects.

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***Introduction:***

Patients who have undergone heart surgery involving extracorporeal circulation (ECC) with global myocardial ischemia induced by aortic clamping show different degrees of transitory ventricular dysfunction without myocardial infarction in the immediate postoperative period. ( Doyle et al 1995)

Despite improvements in surgical technique and myocardial protection, pharmacological support for low cardiac output is often required during and after weaning from cardiopulmonary bypass (CPB). This acute deterioration in ventricular function may continue into the post-anesthesia care unit or intensive care unit (ICU). Because cardiac surgery is conducted in an increasingly aged population, with coexisting pathology, these patients are at increased risk for developing a low cardiac output syndrome (LCOS) during the postoperative period.(Boldt et al 1993)

This dysfunction can cause postoperative low cardiac output syndrome with a prevalence of about 10%. The mortality rate among those who develop this complication is 17 %.(Rao et al 1996)

Myocardial stunning is an acute derangement of contractile function of ischemic myocardium at the moment of restoration of

coronary blood flow by various interventions like bypass grafting, angioplasty or thrombolysis. The pathogenesis of ischemia/reperfusion (IR) injury consists of several mechanisms. Recently, there is increasing evidence for a hyper-contracture during reperfusion induced by high cytosolic Ca2+ levels or by low ATP concentrations.(Moens et al 2005)

On the other hand, the intensity of free radical generation during reperfusion, and hence reperfusion injury, was found to be proportional to the severity of the antecedent ischemia.(Bolli et al 1998)

Treatment includes the administration of positive inotropic drugs and vasodilators, balloon counter-pulsation, and the use of mechanical devices that assist circulation.(Doyle et al 1995)

Ca2q-sensitizers are a different class of drugs that might potentially be used to increase the hearts' ability to contract more forcefully. These could overcome the limited availability of Ca2q that has been shown to occur in heart failure because of decreased sarcoplasmic reticulum calcium uptake and depressed systolic calcium transients. (Hasenfuss et al 1998)

Levosimendan, a positive inotropic drug belonging to the group of agents that increase the sensitivity of contractile proteins to calcium, has recently been introduced. The use of this drug in the treatment of heart failure is based on its double mechanism of action: the improvement of myocardial contractility through the sensitization of troponin C to calcium, and the systemic, pulmonary and coronary arterial and venous vasodilatation induced by activation of the ATP-sensitive potassium channels of smooth muscle fibers. (Jamali et al 1997)

Levosimendan increases cardiac output, coronary and renal blood flow, and heart rate, and reduces the pre- and post load. It also has an anti-arrhythmia effect and can revert myocardial stunning. (Jamali et al 1997)

Unlike agents that act through adrenergic pathways, levosimendan does not cause diastolic calcium overload, which can impair myocardial relaxation, increase energy expenditure, or both. (Haikala et al 1995)

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***List of Abbreviations:***

- (I/R) Ratio: Ischemia–Reperfusion Ratio.
- CI: cardiac index.
- CI: Cardiac Index.
- CPB: cardiopulmonary bypass.
- CS: cardiac surgery
- HR: Heart rate.
- IABP: Intra Aortic Balloon Pumping.
- LCOS: low cardiac output syndrome.
- LVAD: Ventricular Assess Device.
- LVSWI: left ventricular stroke work index.
- MAP: mean arterial pressure.
- mPAP: mean Pulmonary Artery Pressure.
- PCWP: Pulmonary Capillary Wedge Pressure.
- PVR: Pulmonary Vascular Resistance.
- SVI: Stroke Volume Index.
- SVO2: Mixed venous oxygen saturation.
- SVR: Systemic Vascular Resistance.
- VAD: Ventricular Assess Device.

# Patient and Method

After approval of the local ethics committee of King Abdul-Aziz University Hospital and informed written consent from patients included in the study this randomized double blind study was conducted on 50 patients aged between 21 and 60 years old undergoing elective open heart surgery.

All patients included in the study had postoperative left ventricular dysfunction (low cardiac output) which was defined as a cardiac index of less than 2.4 L/min/m2 plus a pulmonary capillary pressure of more than 15 mmHg despite adequate control of heart rhythm, and in the absence of myocardial ischemia, valve dysfunction or cardiac tamponade.

**Inclusion criteria**:

(1) Age from 21 to 60 years old patient.

(2) Undergoing cardiac surgery involving extracorporeal circulation (ECC).

(3) Having post-operative low cardiac output with cardiac index of <2.4 L/min/m2.

**Exclusion criteria**:

(1) Age younger than 21 years; childbearing potential.

(2) Heart failure due to restrictive or hypertrophic. cardiomyopathy or to uncorrected stenotic valvular disease.

(3) Patients with uncontrolled arrhythmias or atrioventricular block of second or third degree.

(4) Severe renal failure (serum creatinine >450 mmol/L).

(5) Hepatic failure; cardiac tamponade; adult respiratory distress syndrome; and septic shock.

(6) Patients receiving long acting vasodilator or inotropic drugs within 24 hrs prior to surgery.

Demographic data, the preoperative diagnosis, the left ventricular ejection fraction in the week before surgery (determined by trans-thoracic echocardiography) and the surgical technique employed were recorded for each subject.

Cardiac medications like digoxin and angiotensin converting enzyme inhibitors (ACEIs) were continued till the morning of the surgery. All patients were premeditated with midazolam 0.1 mg/kg orally on the night before surgery and morphine sulphate 0.1 mg/kg and scopolamine 8 μg/kg i.m. one hour before surgery.

## *Monitoring:*

On arrival to the operating room, under local anesthesia in addition to midazolam 10-20 μg/kg i.v as required, radial artery catheter was inserted. Electrocardiographic monitoring of lead II and $V_5$, pulse oximetry, and invasive arterial pressure monitor were connected before induction of anesthesia.

After anesthetic induction a Swan-Ganz catheter (Opti-Q CCO/SvO2, Abbott Laboratories, IL, USA) was introduced and cardiac output and mixed venous oxygen saturation were determined continuously.

## *Anesthetic and surgical techniques:*

A standard anesthetic technique for all patients was performed. Anesthesia was induced with intravenous fentanyl 5-10 μg/kg and propofol 0.5-1.0 mg/kg. Rocronium 0.4 mg/kg i.v was administered to facilitate tracheal intubation and muscle relaxation. Capnography and body (nasopharyngeal and rectal) temperature were monitored by using a modular monitor (Morquette Solar 8000. USA). Patients were mechanically ventilated with oxygen/air (inspired oxygen fraction 50%) and end tidal carbon dioxide was kept at a range of 30-35 mmHg using the closed circuit

of North American Drager anesthetic machine (Narcomed G5).

Anesthesia was maintained with Sevoflurane (0.5-1.0%) and supplemental propofol 50-100 µg/kg/min throughout the surgery and fentanyl 1-2 µg/kg i.v as required (total dose 20-50 µg/kg allover the surgery). Other boluses of i.v rocuronium were used, as required to maintain the state of muscle relaxation through surgery.

All operations were performed through a median sternotomy using a standard surgical technique. Before aortic cannulation, the patients were anticoagulated with heparin 4 mg/kg to reach ACT 400 seconds. The CPB was conducted with a flat sheet membrane oxygenator using non-pulsatile flow with moderate hypothermia (26-28 °C). The circuit prime consisted of Ringer's solution 1800 ml, 25% mannitol 100 ml and heparin 6001U. The pump flow was maintained at 2.0-2.5 liter/min/m'. Cold cardioplegic solution was given after aortic cross-clamping for myocardial protection.

After weaning from CPB, when the surgery was completed, protamine sulphate was infused slowly over 20 min to neutralize heparin effect. After skin closure, all patients were transferred to ICU, intubated and mechanically ventilated.

## *Study design and measurement:*

All patients were randomly allocated to one of two groups each group contains 25 patients.

***First Group:*** The members of this group were administered 5-7.5 μg/kg/min dobutamine by continuous infusion for 24 h (dobutamine group-**DG**).

***Second Group:*** The members of this group received levosimendan administered as a loading dose of 12 μg/kg over 15-20 min, followed by infusion of 0.2 μg/kg/min for 24 h (Levosimendan group-**LG**)

All patients received study drugs on weaning from CPB and continued for 24 hours.

## *Hemodynamic measurements:*

Heart rate (HR), mean arterial pressure (MAP). mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PC WP), Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and left ventricular stroke work index (LVSWI) were measured before starting the study drug (baseline value), then every 15minutes during first hour, then

at 2 hr, 4 hr and 6 hr 12 hr 24 hr 48 hr after weaning from CPB.

All derived haemodynamic parameters were calculated from standard formulae.

**Statistical Analysis:**

Data were collected and entered into the software SPSS (version 12). The data were expressed as mean ±SD. Chi-square was applied to analyze the nominal data, e.g. sex distribution, preoperative medications. One-way analysis of variance (ANOVA) followed by Tukey-HSD test was used for intra-group comparison between the mean values at different times with base line. Unpaired t-test was used for comparison of variables between both groups. $P \leq 0.05$ was considered statistically significant.

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