The influence of Levosimendan on early postoperative outcome of patients with poor Left Ventricular function undergoing coronary artery bypass grafting using single clamp technique

Hamdy Singab, MD*, Mohamed El Shafei,MD',

Mai Abd el Fattah Madkour,MD''

* Assistant Professor of Cardiac Surgery, Ain Shams university.

' Assistant Professor of Anaesthesia, Ain Shams university.

'' Lecturer of Anaesthesiology, Cairo University

Abstract:

Introduction:

Single clamp on pump coronary artery bypass grafting (CABG) technique is increasingly practiced than traditionally multiple cross clamp technique to prevent the risk of aortic manipulation during multiple clamp technique and it is remarkably used in patients with poor left ventricular function (LV) than off pump technique to avoid the harmful effect of hemodynamic compromise during cardiac positioning. (1)

Although, catecholamines improve the myocardial performance, they increase the myocardial oxygen consumption that increase the risk of development of postoperative arrhythmias and ischemia.(2)

Levosimendan, a calcium-sensitizing agent, is a newer inotropic agent that exerts its effects by binding to troponin C, which increases the sensitivity of contractile proteins to calcium . Levosimendan increases cardiac output, reduces afterload, and decreases cardiac filling pressures.(3)

Administration of Levosimendan enhances cardiac performance both in patients with low-output heart failure and poor LV function, a 24-h administration of Levosimendan (0.1– 0.2µg. kg^{-1}. Min^{-1}) increased cardiac output by 1.09 l/min and decreased pulmonary capillary wedge pressure (PCWP) by 7 mmHg.(4)

Aim of the work of our study is to emphasize that the use of Levosimendan in patients with poor Left Ventricular function undergoing coronary artery bypass grafting using single clamp technique would be associated with better hemodynamics and cardiac function.

Patient and methods:

A total of 60 patients of both sexes with ischemic heart disease with poor cardiac function EF% <40% measured by Transthoracic echocardiography undergoing elective cardiopulmonary bypass grafting were randomly allocated for the study.

Patients were excluded from the study if they had pre-existing renal failure , thrombocytopenia or history of pre-operative use of inotropes or cardiopulmonary rescussitation.Patients were randomly allocated into 2 equal groups each of 30 patients using individual closed envelope randomization as follows :

Group (L): Levosemindan group

Group (A): Adrenaline-Tridil group.

1. All routine preoperative investigations were done including CBC, Coagulation profile, liver function tests, kidney function tests, blood grouping , Chest X-ray, recent echocardiography and cardiac angiography. Postoperative trans oesophageal echocardiography to measure Cardiac output ml/min, PA systolic pressure (PASP) was deduced from this, because it would be equal to RVSP in the absence of pulmonic stenosis (PS) and *Left ventricular systolic function as well as the postoperative* hemodynamic data were collected at 4 intervals :

   (1) Pre-CPB baseline before sternotomy (T0)

   (2) 6 hours after completion of surgery (T1)

   (3) 12 hours after completion of surgery (T2)

   (4) 24 hours after surgery. (T3)

Results :

However In both groups, infusion of Levosimendan and Adrenaline resulted in significant increase in both the systolic blood pressure and the diastolic blood pressure .The systolic blood pressure increased significantly (p = 0.001) in Levosimendan group and the diastolic blood pressure increased significantly (p=0.003) in Levosimendan group after bypass compared to the same time in Adrenaline group.In both groups, infusion of Levosimendan and Adrenaline resulted in significant increase in both stroke volume and cardiac output starting after CPB and continuing until the end of the study.

However, patients in the Levosimendan group has significantly more higher stroke volume(p=0.001) and cardiac output(p = 0.001) relative to those in Adrenaline group starting after infusion of the drug and lasting until the end of study.In Levosimendan & Adrenaline group , the VTI started to increase significantly 10 min post – bypass (relative to baseline) and reach its maximum at the end of the study, this occurred without any significant differences between the both groups throughout the study.The PASP decreased significantly post bypass reaching its lowest value at the end of study, but with no significant difference among both groups. In both Levosimendan and Adrenaline groups, the fraction shortening increased significantly 10 min post-bypass p=0.003, p=0.008 respectively, reaching its maximum at the end of surgery p=0.009,p=0.001 respectively with no significant difference between the 2 groups throughout the study.

Conculusion: our results indicated that levosimendan infusion is the best choice for patients with poor Left Ventricular function undergoing coronary artery bypass grafting using single clamp technique as it associated with better early postoperative haemodynamics,cardiac performance and clinical outcome in terms of rapid recovery of postoperative myocardial stunning period of ICU stay and need for further inotropic agent better than use of the classical inotropic agents period.

Key word: levosimendan,ICU stay, postoperative haemodynamics, CABG with poor LV function

Introduction:

Single clamp On pump coronary artery bypass grafting (CABG) technique is increasingly practiced than traditionally multiple cross clamp technique in an effort to prevent the risk of aortic manipulation as well as it is remarkably used in patients with poor left ventricular function (LV) than off pump technique to avoid the harmful effect of haemodynamic compromise during cardiac positioning, as the atrial displacement below the corresponding ventricle during the exposure of the posterior or the lateral wall will result in remarkable increasing of the atrial pressure and decrease of the cardiac output (COP).(1)

However catecholamine improve the myocardial performance in terms of contractility and COP through increasing of the free intracellular Ca concentration and cyclic adenosine monophosphate, it increases the myocardial oxygen consumption that increase the risk of development of postoperative arrhythmias and ischemia.(2)

Levosimendan, a calcium-sensitizing agent, is a newer inotropic agent that exerts its effects by binding to troponin C, which increases the sensitivity of contractile proteins to calcium . Levosimendan increases cardiac output, reduces afterload, and decreases cardiac filling pressures.(3)

Standard inotropic agents as Adrenaline acts by binding of catecholamines to β_1-adrenergic receptors on the surface of myocytes activates adenylate cyclase, which generates cAMP from ATP. cAMP activates protein kinase A.

Administration of levosimendan enhances cardiac performance both in patients with low-output heart failure and poor LV function, a 24-h administration of levosimendan (0.1– 0.2µg. kg-^{1}. Min^{-1}) increased cardiac output by 1.09 l/min and decreased pulmonary capillary wedge pressure (PCWP) by 7 mmHg.(4)

Although Ca^{2+} sensitizers carry a potential risk of worsening diastolic function, levosimendan decreased the isovolumic relaxation time which indicating improvement rather than deterioration of diastolic function. (6)

Because levosimendan decreased PCWP more effectively than dobutamine, it may be of value in patients with reversibly increased pulmonary pressures or right ventricular dysfunction which may occur in ischemic heart patient with severly impaired left ventricular function. Levosimendan has favourable effects on coronary blood flow by overriding the normal auto-regulatory mechanisms of coronary circulation and thus dilates coronary vessels.*(5)*

Levosimendan improves the coronary autoregulatory mechanisms and dilate the coronary vessel so it increase the coronary blood flow without increase in the myocardial oxygen demand.(7)

Patients and methods:

After the approval of the ethical committee in our institute and obtaining an informed consent from the patients , a total of 60 patients of both sexes with ischemic heart disease with poor cardiac function <40% measured by Transthoracic echocardiography undergoing elective cardiopulmonary bypass grafting were randomly allocated for the study.

Patients were excluded from the study if they had pre-existing renal failure , thrombocytopenia or history of pre-operative use of inotropes or cardiopulmonary rescussitation.

Patients were randomly allocated into 2 equal groups each of 30 patients using individual closed envelope randomization as follows :

Group (L): Levosimendan group

Group (A): Adrenaline-Tridil group.

All routine investigations were done including CBC, Coagulation profile, liver function tests, kidney function tests, blood grouping , Chest X-ray, recent echocardiography and cardiac angiography.

Preoperative medications :

All patients were given Midazolam 0.05mg/Kg prior to cannulation. In the preparation room all patients were monitored using 5 lead ECG electrodes placed on the back, non invasive arterial blood pressure and pulse oximetry. Oxygen was administered via a nasal cannula using 3L/min.

The radial artery of the non- dependant hand was cannulated using a 20 G arterial cannula under local anaesthetic (Lidocaine 2%) and a baseline arterial blood gases (ABG) sample, Random blood sugar (RBS) and activated clotting time (ACT) were done.

The right internal jugular vein was cannulated under local anesthesia using the anterior approach technique with a triple lumen central venous catheter. Patients were then transferred to the operating room.

Induction :

Anaesthesia was induced using Thiopental sodium 2-3mg/kg, Fentanyl 3-5 mcg/kg. Following induction of anaesthesia end- tidal CO2 cable was attached and oropharyngeal temperature probe was inserted. Tracheal intubation was facilitated using Succinyl Choline 1mg/kg followed by pancuronium 0.1mg/kg and anaesthesia was maintained by Sevofluorane 1-2% in O2/Air mixture and Fentanyl infusion 1-2 mcg/Kg/h.

Lungs were mechanically ventilated, where tidal volume and respiratory rates were adjusted to maintain end tidal CO2 35-45 mmHg and FiO2 maitained at 0.5.

A 7.5-MHz multiplane TEE probe and system (Vivid 3, GE Medical Systems, Milwaukee, Wis) will be used for all echocardiographic measurements. All patients underwent a complete transesophageal echocardiography examination (TEE) according to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists (ASE/SCA) guidelines.

During re-warming and after release of aortic cross clamp, the selected patient to receive either Adrenaline (A group) a dose of 0.01-0.2 mg/Kg/min

or Levosemindan (L group) loading dose 6–24μg/kg of bolus administration over 10 min, followed by a continous infusion of 0.05–0.2μg/kg/min .Heparin is reversed using protamine in a dose 1-1.5 times the heparin dose, the reversal of heparin is checked by ACT.

Preioperative Demographic data including age, gender, height, weight, BSA, hypertension ,hyperlipedemia,diabetes , previous MI , use of β-blockers, ischemic time and bypass time were recorded for each patient. In addition to the standard anesthetic record, an independent observer recorded MAP , HR ,PASP , COP and FS.

Transoesophageal echocardiography and hemodynamic data were collected at 4 intervals :

(1) Pre-CPB baseline before sternotomy (T0)

(2) 6 hours after completion of surgery (T1)

(3) 12 hours after completion of surgery (T2)

(4) 24 hours after surgery. (T3)

2. Cardiac output ml/min. The cardiac output was calculated with the aid of transesophageal echo-Doppler as follow

    1. CO = Left ventricle stroke volume X heart rate
    2. Stroke Volume = Stroke Distance (VTI) X cross sectional area (CSA)
    3. VTI was calculated with continuous wave Doppler (CW) beam directed through aortic valve orifice from TG long axis or deep transgastric long axis view.
    4. The CSA of the aortic valve was estimated by planimetry of equilateral triangle shaped orifice observed in mid-systole.
    5. RV and PA Systolic Pressure. For quantitative assessment of RVSP, the peak tricuspid regurgitant (TR) jet velocity, obtained on continuous wave Doppler, was used to calculate peak pressure gradient between the RV and RA during systole using the modified

Bernoulli's equation (1). RVSP was then calculated by adding estimated RAP to the measured gradient. PA systolic pressure (PASP) was deduced from this, because it would be equal to RVSP in the absence of pulmonic stenosis (PS).

6. Diastolic function of the RV was measured by the E/A ratio .

1. *Left ventricular systolic function*
2. Fractional shortening (FS) will be obtained in trans-gastric mid papillary short axis view. FS is obtained by measuring LV end-diastolic dimension (LVEDD) and LV end-systolic dimension (LVESD) on M-mode

FS(%) = ([LVEDD - LVESD] / LVED

Operative technique:

Median sternotomy and pericardiotomy

All Patients were operated upon under cardiopulmonary bypass perfusion {CPB }after standard aortic and atrial double stages venous cannulation. moderate hypothermia (28 - 30 ºc), The aorta was totally cross clamped and myocardial preservation was achieved via an antegrade cold enriched blood cardioplegia. A single clamp technique where both the distal anastmosis (graft to coronary) and the proximal anastomosis (graft to aorta) were done with only single aortic clamp and there are no need for the standard multiple partial aortic clamp. After finishing of each proximal anastomosis the aortic venting was stopped till we started to do the next distal anastomosis.

All patients had LIMA to LAD anastomosis.

After de-airing rewarming and aoric declamping we started mechanical ventilation and cardiac inotropic support was started as follows:

Group A: Adrenaline a dose of 0.01-0.2 mg/Kg/min

or

Group L: Levosimendan (L group) loading dose 6–24µg/kg of bolus administration over 10 min, followed by a continous infusion of 0.05–0.2µg/kg/min.

Heparin is reversed using protamine in a dose 1-1.5 times the heparin dose, the reversal of heparin is checked by ACT.

After completion of surgery , the patient was transferred to ICU for elective ventilation .

Postoperative variables including ICU stay and duration of ventilation were also measured , as well as postoperative Troponin , CKMB were measured at 6 hrs, 12hrs and 24 hrs after the end of surgery . Serial blood gases were done to measure serum lactate levels in ICU. Postoperative delayed sternal closure, rexploration for bleeding, need for increased intropes, IABP and total hospital stay were measured.

Statistical analysis was done using SPSS Statistics version 13. Data was presented as mean (±SD) or numbers (%).The distribution of categorical variables among patient groups analyzed by Chi-Square test or Fisher's exact test,were applied as indicated.. Means were compared with the unpaired or paired Student's test, as indicated. P values of 0.05 or less were considered as being statistically significant.

Results :

Table 1:Preoperative demographic criteria

Variables	Group A 30 patients	Group L 30 patients	P value
Age	55±6.3	53± 8.1	0.28
Gender Male:Female	24/6	20/10	0.12

Height in meter	160±15.8	156±17.2	0.37
Weight in Kg	85±10.9	86 ±10.2	0.161
BSA	1.9±0.31	1.82±0.26	0.98
Diabetes	22	24	0.407
Hypertension	22	24	0.151
Hyperlipedemia	24	16	0.121
Previous MI	8	6	0.67
Unstable angina	6	7	0.64
EF	36±3.4	38±2.3	0.65
LVEDD	6.5±o.9	6.3±0.804	0.142
LVESD	5.45±0.902	5.4±0.88	0.1
Single vessel	0	0	0.6
Two vessels	10	12	0.705
Three vessels	20	18	0.704
Use of B blockers	25	26	1
Use of ACI inhibitors	12	14	0.72

Table 2:Operative variables

Variables	Group A 30 patients	Group L 30 patients	P value
Aortic cross clamp Time (in minutes)	55 ± 21.27	58.3 ± 12.24	0.2
Total Bypass time (in min)	80.12 ± 21.51	76 ± 12.65	0.06
Adrenaline (% of patient)	100%	0	
Nor adrenaline (% 0f patient)	6.7%	60%	0.02 †
Levosemindan	0	100%	
LADgrafts	100%	100%	
D1 grafts	80%	60%	0.08
OM grafts	63%	72%	0.34
RCA grafts	14%	12%	0.71
PDA grafts	64%	66%	1.02
Ventilation time (in hour)	10.5±1.5	10±1.9	0.17
ICU stay (in days)	4.5±0.7	4.3±0.8	0.06

However the use of noradrenaline in L group was significantly higher than A group intraoperatively,The other demographic and intra-operative data were comparable between without any significant differences between both groups .

Table 3:Postoperative & Hemodynamic variables

variables	Group	T0 Baseline	T1 6 h	T2 12h	T3 24h
SBP(mmHg)	A	105±7.8	95±5.5	97±6.6	105.5±9.3 †‡
	L	108±6.5	97±4.5	98.5±5	120±8*†
P value		0.608	0.167	0.94	0.001
DBP(mmHg)	A	52± 5.1	55±2.6	40.5±4.7	43.5± 4.2
	L	54± 6.3	56±3.5	45.5±3.2	52±6.1*
P value		0.52	0.55	0.11	0.003
MAP(mmHg)	A	75±8.03	80±5	79±9.3	84±6.3
	L	80±8.5	75±6.8	80±8.3	85±5.9
P value		0.12	0.22	0.94	0.24
HR	A	67±12.8	98±15	101±17	95±12.4
	L	65±12.9	92±19	95±16	98±12
Pvalue		0.729	0.42	0.288	0.17
VTI (cm/sec)	A	7.53±5.7	8.35± 5.7	10.6±7.9 †	12.1±9.8 †‡
	L	7.32±5.5	7.35±1.08	11.7 ±5.5†	10.95±7.3 †‡
P value		0.212	0.67	0.142	0.05
SV (ml/min)	A	11.6±2.3	10.7±4.9	12.8± 7.5 †	14.5±9.8 †‡
	L	10.1±1.7	10.9±2.8	17.6 ±11.78 *†	22.7± 9.2 *†‡
P value		0.42	0.141	0.001	0.001
COP (litres)	A	4.96±0.76	5.13±0.s64	5.32±0.96 †	5.89±0.25 †‡
	L	5.13±0.63	5.22±0.42	6.66±0.75 *†	6.84±0.55*†
P value		0.5	0.46	0.0001	0.001
PASP (mmHg)	A	55±13.03	52.5±4.5	45± 2.7 †	40±6.2 †‡
	L	60±10.6	62±4.9	50±4.8 †	38± 7.5 †‡
P value		0.212	0.21	0.78	0.121
$ScvO_2$ %	A	60±2.7	58±3.7	68.5±4.7 †	75.5±8.2†‡
	L	63±3.2	61.5±3.6	66±5.7 †	72.5±8 †‡*
P value		0.67	0.41	0.05	0.005
FS	A	18±1.86	18.7±2.3	25±3.2 †	31.5±2.6†
	L				

	17.5±2.6	22±2.5	23.55±2.3†	33.8±4.9†‡
P value	0.221	0.54	0.6	0.12

*statistically significance ($p<0.05$) comparing the two groups at the same time

‡ statistically significance ($p<0.05$) comparing T_2 to T_3 in same group

There was no significant differences in the baseline hemodynamic values among groups.

However In both groups, infusion of Levosimendan and Adrenaline resulted in non significant increase in both systolic blood pressure and the diastolic blood pressure in both groups in the early postoperative hours, there was a significant increase in both The systolic blood pressure and the diastolic blood pressure in Levosimendan group at 24 hour after bypass compared to the Adrenaline group at the same time ($p = 0.001$ & $p=0.003$ respectively).

In both groups, infusion of Levosimendan and Adrenaline resulted in a non significant increase in both stroke volume and cardiac output in the early hours postoperatively there was a significant increase in the stroke volume and the cardiac output starting after 12 hour of cessation of the bypass and continuing until the end of the study ($p=0.001$ & $p=0.001$ respectively)

In both groups , the VTI started to increase significantly post – bypass (relatively to the baseline) and reach its maximum at the end of our study(24hours post-bypass), this occurred without any significant differences between the both groups throughout the study .

The PASP decreased significantly post-bypass in both groups and reaching its lowest value at 24 hours post-bypass, with a non significant difference among both groups.

In both both groups, the fraction shortening increased significantly post-bypass and reaching its maximum at (24 hours post-bypass) the end of study with no significant difference between the two groups .

However In both groups $ScvO_2$ increased progressively starting from post-bypass till the end of our study,it was maintained throughout the procedure with a non significant difference between the two groups except at the end of the study it shows a significant difference between the two groups ($p=0.005$).

Table 4:postoperative variables

A.

Variables	Group	T1 Baseline	T2 6 h	T3 12h	T4 24h
Troponin(ng/ml)	A	1±0.60	1.3±0.67	1.1±0.76	0.76±0.15
	L	1.2±0.67	1.24±0.56	1.26±0.19	0.82±0.24
P value		0.7	0.121	0.2	0.2
CK MB	A	42.2±3.5	47.2±2.8	31.6±4.2	21.6±3.2
	L	41±3.3	46±2.1	29.8±1.3	23.2±1.2
P value		0.121	0.5	0.40	0.12
Serum lactate	A	2.1±0.45	2.5±0.95	2.2±1.1	2.1±0.75
	L	1.8±0.49	2.2±0.57	1.8±0.46	1.9±0.65
P value		0.11	0.281	0.26	0.42

There were no significant differences in the perioperative troponin, CKMB and serum lactate levels between the two groups.

B.

Variables	Group A	Group L	P value
IABP	15%	22%	0.005
Needs of inotropes	45%	13%	0.001
Delayed closure of sternotomy	30%	28%	0.67
reopening	14%	15%	0.7
Hospital stay(days)	8±5.46	7±5.8	0.6

Postoperative data were comparable between both groups, without any significant differences between the 2 groups, however, IABP and needs of more inotropes increased significantly (p=0.005) and (p =001) respectively in Adrenaline group after bypass compared to the same time in Adrenaline

group. The reopening and hospital stay shows no significant difference between the 2 groups throughout the study.

Discussion:

In spite of myocardial preservation during CABG there was a variable degree of postoperative myocardial stunning, which appeared as a state of prolonged post-ischemic myocardial dysfunction that was rescued by myocardial reperfusion (8).however several literatures noted that the early postoperative myocardial dysfunction in the first few hours postoperatively disappeared spontaneously over 24-48 hours, the period of temporary postoperative myocardial stunning need an inotropic agent to improve its function. (9&10)Unlike Several classical inotropic agents used for myocardial support in the early postoperative period included adrenaline and nor adrenaline that act by binding of catecholamines to β_1-adrenergic receptors on the surface of myocytes that activate the adenylate cyclase, which generates cAMP from ATP. cAMP activates protein kinase A., Levosimendan, a calcium-sensitizing agent, is a newer inotropic agent that exerts its effects by binding to troponin C, which increases the sensitivity of contractile proteins to calcium without increasing its intracellular concentration. Levosimendan increases cardiac output without an increase in the myocardial oxygen consumption, reduces afterload by systemic vasodilatation as a result of activation of k ATP channel associate with decreasing of calcium sensitivity and decreases cardiac filling pressures. (3&12)recent studies demonstrated that Levosimedndan increase

the coronary blood flow and reduce the coronary vascular resistance.(13) although Levosimendan has a short half life(1hour), its active metabolite has a long life (70-80 hours). Administration of Levosimendan enhances cardiac performance in patients with low- cardiac output, a 24-h administration of Levosimendan (0.1– 0.2µg. kg^{-1}. Min^{-1}) increased cardiac output by 1.09 l/min and decreased pulmonary capillary wedge pressure (PCWP) by 7 mmHg.Because Levosimendan decreased PCWP more effectively than dobutamine,it may be of value in patients with reversibly increased pulmonary pressures or right ventricular dysfunction which may occur in ischemic heart patient with severly impaired left ventricular function.(12,13,14)

Levosimendan advantages over the classical inotropes are long drug effect after 24 hour infusion up to 9 days, lack of postoperative arrhythmias, absence of drug induced postoperative myocardial ischemia, promote the recovery of stunned myocardium and decrease the size myocardial infarction of as a result of k (ATP) channel activation in the ventricular and arterial wall. (15)

Most of Levosimendan disadvantages are dose related and include headache, hypotension dizziness and nausea. A profound hypotension after a bolus dose of Levosimendan was noted as the main disadvantage of its using and demanding avoiding of its bolus dose.(16)

In our study we give a loading dose 6–24µg/kg of levosimendan over 10 min, followed by a continous infusion of 0.05–0.2µg/kg/min in levosiemndan group. Noradrenaline infusion to maintain MAP > 70 mmHg was significantly required patient of L group to maintain MAP > 70 mmHg.

Our results are in agreement with the findings reported by recent studies in the same issue that show a significant increase of COP produced by levosimendan as a result of its combined actions of reduced after load and increased cardiac contractility in comparsion of classical inotropic agents.

Our study has several limitations, the cardiac index , systemic vascular index and pulmonary capillary wedge pressure were not measured.

In conclusion, our results indicated that levosimendan infusion is the best choice for patients with poor Left Ventricular function undergoing coronary artery bypass grafting using single clamp technique as it associated with better early postoperative haemodynamics,cardiac performance and clinical outcome in terms of rapid recovery of postoperative myocardial stunning period of ICU stay and need for further inotropic agent better than use of the classical inotropic agents period.

References :

1- Atasever B, Boer C, Speekenbrink R, Seyffert J, Goedhart P, de Mol B. *et al.* Cardiac displacement during off-pump coronary artery bypass grafting surgery: Effect on sublingual microcirculation and cerebral oxygenation. Interact Cardiovasc Thorac Surg 2011;13:573-7.

2-Wu X, Bers DM. Sarcoplasmic reticulum and nuclear envelope are one highly interconnected Ca2+store throughout cardiac myocyte. Circ Res 2006;99:283-91.

3-John Lynn, Novel medical therapies for pediatric heart failure, progress in pediatric cardiology 2007 :23: 61-66

4- *Follath F, Cleland JG, Just H et al: Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomised double-blind trial. Lancet 2002; 360:196–202*.

5- J. Lilleberg, M. S. Nieminen et al , Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary arterybypass grafting.* Eur Heart J, Vol. 19, April 1998

6-Sonntag S, Sundberg S, Lehtonen LA et al: The calcium sensitizer levosimendan improves the function of stunned myocardium after percutaneous transluminal coronary angioplasty in acute myocardial ischemia. J Am Coll Cardiol 2004; 43:2177–82.

7- 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.

8-Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. J Clin Invest increased myocardial performance after surgery1975;56:978-85.
9-Breisblatt WM, Stein KL, Wolfe CJ, Follansbee WP, Capozzi J, Armitage JM, *et al*. Acute myocardial dysfunction and recovery: A common occurrence after coronary bypass surgery. J Am Coll Cardiol 1990;15:1261-9.
10-Ukkonen H, Saraste M, Akkila J, Knuuti MJ, Lehikoinen P, Någren K, *et al*. Myocardial efficiency during calcium sensitization with levosimendan: A noninvasive study with positron emission tomography and echocardiography in healthy volunteers. Clin Pharmacol Ther1997;61:596-607.
11- Gruhn N, Nielsen-Kudsk JE, Theilgaard S, Bang L, Olesen SP, Aldershvile J.
Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-sensitizing properties. J Cardiovasc Pharmacol 1998;31:741-9.
12-Ukkonen H, Saraste M, Akkila J, Knuuti J, Karanko M, Iida H, *et al*.Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther 2000;68:522-31.
13- Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003;107:81-6.
14- McLean AS, Huang SJ, Nalos M, Ting I. Duration of the beneficial effects of levosimendan in decompensated heart failure as measured by chocardiographic indices and B-type natriuretic peptide. J Cardiovasc Pharmacol 2005;46:830-5.
15-Kersten JR, Montgomery MW, Pagel PS, Warltier DC, *et al.* levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K (ATP) channels. Anesth Analg 2000;90:5-11.
16-sandell EP,Wesby-van-Swaay E,Poder P,T,Sarapohja MS,Nieminen and L.lethonoen.341 ametaanalysis on the safety of the calcium sensitizing agent levosimendan.Eur J Heart Fail Suppl 2004;3:86.