***The Role of Levosimendan As Inotropic Agents In Patients With LV Dysfunction Admitted To ICU Post Cardiac Surgery***

***Thesis***

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# List of Abbreviations

**AA:** Arachidonic acid

**AAD:** Antiarrhythmic Drug  
**ACS:** Acute Coronary Syndrome  
**ADP:** Adenosine Diphosphate  
**AF:** Atrial Fibrillation  
**AFL:** Atrial Flutter  
**APTT:** Activated Partial Thromboplastin Time  
**ASA:** Acetylsalicylic Acid  
**AV:** Atrioventricular  
**AVNRT:** Atrioventricular Node Re-entry Tachycardia  
**AVRT:** Atrioventricular Re-entry Tachycardia  
**BMS:** Bare Metal Stent  
**CABG:** Coronary Artery Bypass Graft  
**CAD:** Coronary Artery Disease  
**CAIC:** Canadian Association of Interventional Cardiology

**CASS**: Coronary Artery Surgery Study  
**CCB:** Calcium Channel Blockers  
**CCS:** Canadian Cardiovascular Society  
**CI:** Confidence Interval

**CHF:** Congestive Heart Failure  
**CKD:** Chronic Kidney Disease`  
**COPD:** Chronic Obstructive Pulmonary Disease  
**CrCl:** Creatinine Clearance  
**CV:** Cardioversion

**CVA**: cerebrovascular accidents  
**DES:** Drug-Eluting Stent  
**DTT:** Diluted Thrombin Time  
**ECG:** Electrocardiogram  
**ECT:** Electroconvulsive Therapy  
**ED:** Emergency Department  
**EF:** Ejection Fraction  
**HF:** Heart Failure  
**Hx:** History  
**ICU:** Intensive Care Unit

**INR:** International Normalized Ratio

**IRB:** Institutional Review Board  
**LA:** Left Atrium  
**LAA:** Left Atrial Appendage  
**LAD:** Left Anterior Descending Artery  
**LIMA:** Left Internal Mammary Artery

**LMWH:** Low Molecular Weight Heparin  
**LV:** Left Ventricle  
**LVEF:** Left Ventricle Ejection Fraction  
**MI:** Myocardial Infarction  
**MVR:** Mitral Valve Replacement  
**NOAC:** Non-Vitamin K Antagonist Oral Anticoagulant  
**NSAIDS:** Nonsteroidal Anti-Inflammatory Drugs  
**NSTEACS:** Non ST-Elevation Acute Coronary Syndrome  
**NVAF:** Non-Valvular Atrial Fibrillation.   
**OAC:** Oral Anticoagulant  
**P-Gp:** P-Glycoprotein  
**PAD:** Peripheral Artery Disease  
**PALLAS:** Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy Trial

**PASS:** Power Analysis and Sample Size System  
**PCI:** Percutaneous Coronary Intervention  
**PIP:** “Pill-in-the-Pocket”  
**PIP-AAD:** “Pill-in-the-Pocket” Anti-Arrhythmic Drug  
**POAF:** Postoperative Atrial Fibrillation  
**QOL:** Quality of Life  
**RCA:** Right coronary artery

**RCT:** Randomized Controlled Trial  
**SAF:** Severity of Atrial Fibrillation

**STEMI:** ST-Elevation Myocardial Infarction  
**TEE:** Trans-Esophageal Echocardiography  
**TIA:** Transient Ischemic Attack  
**TT:** Thrombin Time  
**TTR:** Time in Therapeutic Range  
**UFH:** Unfractionated Heparin  
**VF:** Ventricular Fibrillation

Introduction

Coronary artery bypass graft (CABG) surgery is the standard of care for the management of patients with three-vessel and left main coronary artery disease (CAD) with viable myocardium, The optimal strategy for management of patients with CAD and severe left ventricular (LV) dysfunction [ejection fraction (EF) ≤ 40%] is not clear, However several studies have demonstrated reduced operative mortality and improved short and long-term survival benefits following CABG among patients with severe LV dysfunction **(Levin R.; 2012).**

Positive inotropic agents are the treatment of choice in patients with LV dysfunction post CABG. Levosimendan is a relatively new drug that was approved initially for the management of LV dysfunction through increasing the sensitivity of cardiomyocyte to intracellular calcium. Levosimendan increases the sensitivity of cardiomyocyte to intracellular calcium by binding to troponin C (**Baysal; 2014**).

Achieving an inotropic effect without increasing intracellular calcium levels can prevent an increased risk of cardiac arrhythmia with this agent. Levosimendan also has vasodilatory properties by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle, causing their relaxation. This mechanism reduces the preload and afterload which is helpful in treating patients LV dysfunction post cardiac surgery. It may also have some phosphodiesterase (PDE) inhibitor activity (**D.V. Nielsen; 2014**).

Starting levosimendan infusion preoperatively or after induction of anesthesia that significantly reduced incidence of low cardiac output syndrome, need for Intraaortic balloon pump (IABP), intubation time and length of ICU stay.

Levosimendan is characterised by a triple mechanism of action; i.e., it acts via calcium-dependent binding to cardiac troponin C, and opens the KATP channels on smooth muscle cells in the vasculature, and in cardiac mitochondria. This binding of levosimendan to troponin C and the opening of KATP channels on smooth muscle cells in the vessels result in its inotropic and vasodilatory effects, respectively, while the opening of KATP channels in cardiac mitochondria is believed to be a cardioprotective pathway (**Zangrillo; 2016).**

The definition of cardioprotection, however, is very broad, and it can be divided into at least two categories of effects: short-term and long-term cardioprotection. Short-term cardioprotection encompasses effects such as preconditioning, postconditioning, and anti-stunning, as well as anti-ischaemic effects. Long-term cardioprotection, on the other hand, is often referred to as having anti-remodelling, anti-apoptotic and anti-inflammatory effects **(R.K.Kodalli; 2013**).

Thus, clinical studies show that levosimendan effectively improves general and pulmonary haemodynamics in patients undergoing cardiac surgery, thereby reducing the need for inotropic agents and mechanical circulatory support, and additionally optimising renal and hepatic function. In general, the length of stay on the ICU and in the hospital is shortened. Overall, levosimendan treatment is considered as a kind of “safety net” in the surgical setting. The unique inotropic and cardioprotective properties of levosimendan can provide sustained effects for several days and can thus help to reduce complications in the postoperative period. On the other hand, vasodilation occurs with this treatment, which can necessitate the administration of vasopressors (**Zangrillo; 2016).**

Aim of the Work

The aim of this study was to determine the effect of levosimendan on the outcomes of patients with LV dysfunction undergoing CABG in terms of

1. Post-operative Mortality.
2. Incidence of arrhythmia.
3. Postoperative LV function by Echocardiography.
4. Incidence of complications eg. Neurological, cardiac & renal.
5. Need for IABP & Length of ICU stay.

Chapter I: Coronary Artery Bypass Grafting

Coronary artery bypass grafting (CABG) is an “open-heart surgery in which a section of a blood vessel is grafted from the aorta to the coronary artery to bypass the blocked section of the coronary artery and improve the blood supply to the heart.” pathophysiology of coronary artery disease was identified in 1876 when it was postulated that angina (imbalance of coronary perfusion supply and demand) was caused by interruption of coronary blood supply and that myocardial infarction occurred after the occlusion of at least one coronary artery(**Diodato & Chedrawy**, **2014**).

The 1960s saw great advances in coronary artery surgery. **Goetz et al.** (**1961**) performinD the first successful human coronary artery bypass operation . **Proudfit et al.(1966)** produced the first practical cardiac angiography visualizing the coronary arteries. In the 1980s, the prevalence of CABG increased and safety improved. Thoracoscopic harvesting of the IMA was reported in 1998 by **Duhaylongsod et al.** Minimally invasive and robotic surgery were also developed(**Poffo et al.**, **2017**). The number of CABG is declining from a peak of 519,000 cases in 2000 to about 300,000 operations in 2012(**Diodato & Chedrawy**, **2014**).

Although the fundamental basis of CABG is to reestablish perfusion to the myocardium, there are different approaches to get this aim . The first factor is the utilization of cardiopulmonary bypass or “on pump versus off pump.” Initially, most cardiac surgeries were done on a beating heart, but with the development of cardiopulmonary bypass and cardioplegia, most CABG were done on pump. Off-pump coronary artery bypass (OPCAB) surgery had regained interest in 1990s. **Benetti et al.**(**1991**) **and Buffalo et al.**(**1996**) Did 2000 OPCAB patients with operative safety. Benefits of OPCAB are lower end organ damage, that is, renal failure, cerebrovascular accidents (CVA), fewer cognitive deficits, less psychomotor defects, less transfusion rates, and less systemic inflammation(**Parissis et al.**, **2015**).

**Afilalo et al. (2012)** published a meta-analysis comparing on-pump CABG and OPCAB. The primary outcomes were all-cause mortality, stroke, and myocardial infarction. Fifty-nine trials were included with nearly 9000 patients. The study population had a mean age of 63.4 years with a male to female predominance of over 4 : 1. Postoperative CVA was significantly reduced by 30% in the OPCAB group (risk ratio (RR) 0.70, 95% CI: 0.49–0.99). Rate in mortality (RR: 0.90, 95% CI: 0.63–1.30) and myocardial infarction (pooled RR: 0.89, 95% CI: 0.69–1.13) were not different between groups. In the metaregression analysis, clinical outcome was similar regardless of mean age, proportion of females in the trial, number of grafts per patient, and trial publication date.

**In 2011**, **Forouzannia et al.** compared clinical and economic outcomes of off-pump and on-pump CABG surgery. They analyzed 304 patients undergoing coronary artery bypass surgery and were randomized into conventional on pump and off-pump groups. On-pump coronary artery bypass OPCAB surgery significantly reduced the need for P.O. transfusion requirement (*P* < 0.05). There were no statistically significant differences in surgical reexploration or length of stay. The mean cost for an on-pump surgery was significantly higher than an off-pump surgery.

**Yadava et al.**, (**2011**) reviewed 3500 patients over 8 years. Women were 14.6% . In-hospital mortality was higher in women as compared to men; 2.92% versus 1.8%. The most common causes of mortality were low cardiac output and renal failure. Use of OPCAB reduced mortality (1.84% versus 4.5% on pump;  *P* =0.01) in women. Blood transfusions (2.5 ± 1.2 units versus 4.3 ± 1.4; units *P* < 0.001); ICU stay (29.4 ± 16.4 h versus 38.3 ± 17.3 h;  *P* < 0.0001); and length of stay (6.81 ± 1.6 d versus 8.05 ± 2.1 d; *P* < 0.0001) were also reduced in OPCAB females.

The randomized on/off bypass (ROOBY) trial Studied the outcomes for 2.203 patients (99% men) at 18 Veterans Affairs Medical Centers. The primary short-term endpoint, adeath or complications within 30 days of surgery, occurred with similar frequency (5.6% for on-pump CABG; 7.0% for off-pump CABG; *P* = 0.19). The primary long-term endpoint, death from any cause, revascularization procedure, or nonfatal myocardial infarction (MI) within 1 year of surgery, occurred more in off-pump CABG (9.9%) than in those having on-pump CABG (7.4%; *P* = 0.04). Neuropsychological outcomes were not different between the groups, and graft patency was higher in on-pump group (87.8% versus 82.6%; *P* = 0.01) at 12 months(**Shroyer et al.**, **2009**).

Minimally invasive and robotic assisted approaches are emerging. Minimally invasive cardiac surgery does not use CPB and can be performed through smaller incisions. This approach has gained popularity and is often used for LIMA to LAD grafts. Other benefits include reduced operative time, reduced recover time, decreased need for blood transfusion, less anesthesia time , decreased length of ICU stay, less pain, and an estimated 40% savings over conventional CABG. However, the total number of bypassable vessels is reduced secondary to exposure making these approaches useful for certain group of patients(**Pettinari et al.**, **2017**).

1. **Indications:**

The CABG procedure is indicated for relief of symptoms (primarily angina) unresponsive to medical treatment or percutaneous transluminal coronary angioplasty (PTCA), specially if operation will delay unfavorable events (death, MI, angina recurrence) more than other treatment. For angina relief, surgery often succeedes where medical or interventional therapy fails or not recommended. For survival, the situation is more complex. There is g agreement that CABG improves prognosis in early post-surgical years in those patients with symptomatic left main coronary artery stenosis or stenosis of three main coronary vessels, although this advantage is not significant after 10–12 years(**Maier**, **2012**).

For majority of patients with less severe pathology, the prognosis is good without surgery. Furthermore, cardiac surgery has advanced mortality have declined dramatically. Thus, selection among different courses of cardiac therapy is based mainly on measures of quality of life (QOL), including minimization of pain and disability(**Diodato & Chedrawy**, **2014**).

1. **Outcomes of CABG:**

Prolongation of life as an outcome of CABG was addressed in 3 randomized clinical trials that compared CABG with medical therapy. They include the Veterans Administration Study (VAS), the European Coronary Artery Surgery Study (ECASS), and the Coronary Artery Surgery Study (CASS). The VAS recruited 1015 patients from 13 centers between 1970 and 1974. Patients were randomly allocated to medical or surgical treatment. There was revealed no significant difference in mortality 4 years after CABG in patients with 1, 2- or 3-vessel disease, but a highly significant increase in survival in patients underwent CABG for left main coronary artery obstruction. The 4-year mortality for CABG patients was 7% (n = 46), compared with 33% for medical treatment (n = 44)(**VA Coronary Artery Bypass Surgery Cooperative Study Group**, **1992**).

The ECASS recruited 768 men below 65-years between 1973 and 1976. Patients were randomized to medical or surgical treatment. The main weakness of this trial was that nothing was known about the original population from which patients were drawn. There was significant improvement in survival for the total CABG population, and for patients with 3-vessel disease, with stenosis in the proximal third of the LAD artery, or with left main coronary disease. After 5 years of follow up, 30 deaths were reported among the 395 patients treated surgically (7.6%), and 61 deaths among the 373 patients treated using medical by (16.3%)(**European Coronary Surgery Study Group**, **1982**).

The CASS recruited 780 patients below 65 years allocated to medical or surgical treatment between 1975 and 1979 (90% male). The 5-year survival in the medical group (92%) and the surgical group (95%) were similar. No significant differences in survival were found between medically and surgically treated groups at baseline in extent of coronary heart disease (CHD) or in ventricular function. In patients with 3-vessel disease and low ejection fractions, a distinct (but not significant) trend for improved 5-year survival was observed in surgical patients (90%) compared with medical patients (80%). This difference reached statistical significance when the 7-year survival was 88% in surgical patients and 65% in medical patients (**Hampton**, **1984**).

For early studies, there were methodological issues . First, there were few females, and there may be a gender difference in outcome following surgery. Second, patients in these studies represented only 20% of the total coronary artery disease population, and thus results cannot be extrapolated to entire population. Third, CABG procedure has advanced significantly, so that operative mortality is much lower than reported in the early trials,   
at **<** 3% for routine CABG(**Ferguson et al.**, **2002**)

One procedural change in CABG is the routine use of internal mammary artery as a conduit for revascularizing the coronary arteries, this is because 10 years after CABG, three quarters of vein conduits are blocked or severely diseased, whereas **>** 90% of internal thoracic artery grafts are patent and disease free. Vein graft failure leads to reduced survival, recurrent angina, late MI, and the need for further intervention. So by 10–15 years after the initial operation, up to 40% of patients may require redo CABG with increased risk and cost. Thus, studies suggest that the use of the left internal thoracic artery to the LAD coronary artery is the most important factor for survival and reduction of late cardiac complications after CABG(**Alexandrovna et al.**, **2017**).

Although there are no randomized trials of total arterial revascularization compared with conventional surgery, studies reported that multiple arterial revascularization offers survival advantages over a single internal thoracic artery graft. In a meta-analysis of about 16 000 patients comprising 11 269 single and 4693 bilateral internal thoracic artery patients matched for age, gender, left ventricular function, and diabetes, the bilateral internal thoracic artery group had significantly better survival (HR for death 0.81, 95% , CI 0.70–0.94)(**Cameron et al.**, **1996**).

Up to 25% of CABG operations are performed off-pump. Non-randomized studies have shown off-pump CABG is safe as on-pump surgery, and in experienced hands has less early complications, in patients with significant comorbidity. In high-risk patients specially those with renal impairment, postoperative renal support is less likely in off-pump surgery, and in patients **>** 70 years, with reduction in incidence of cerebral injury. However, randomized trials did not reveal a significant reduction in morbidity or mortality(**Pepper & Chir**, **2005**).

In parallel with the progress of the revascularization techniques for patients with stable angina, several randomized trials were performed comparing: medical management with surgery; medical management with PTCA or percutaneous coronary intervention (PCI); and PCI with surgery(**Foussas & Tsiaousis**, **2008**; **Park & Park**, **2012**; **Sandoval et al.**, **2015**). In a review of seven trials, survival was greater in high risk patients following CABG compared with medical treatment, where patient risk was defined by severity of ischemia, number of diseased vessels, and left ventricular dysfunction. In low-risk patients, a strategy of initial medical therapy was effective (**Spargias & Cokkinos**, **2004**).

Overall, studies indicate that patients with narrowing of the left main coronary artery, or triple-vessel disease and subnormal left ventricular functioning have poor prognosis when treated medically, and benefit from CABG(**Fajadet et al.**, **2019**; **Ramadan et al.**, **2018**). Studies suggest that the use of left internal thoracic artery to left anterior descending coronary artery, and potentially multiple arterial revascularization, improves survival and reduces late cardiac events after CABG. Also, off-pump CABG may offer fewer early complications, particularly in patients with significant comorbidity(**Al-Hijji et al.**, **2018**). Data are less clear for patients with single- or double-vessel disease, or with normal left ventricular functioning. For these patients, many variables (including the patient's level of physical functioning, psychological functioning, social functioning, and vocational status) must be taken into account when considering the benefits of surgery (**Alexandrovna et al.**, **2017**).

Improved functional status and return to pre-morbid lifestyle is a major goal for most patients undergoing CABG. Relief of angina and dyspnea, level of physical activity, complications of surgery, and re-hospitalization are to be investigated when assessing physical function(**Diodato & Chedrawy**, **2014**).

Incapacitating angina is the most common indication for CABG. Observational studies and randomized controlled trials of medical versus surgical treatment found that in patients with disabling angina pectoris, surgery results in relief from symptoms and decreased need for anti-anginal medication(**Reenan**, **2004**). A review of 14 controlled clinical trials demonstrated that the possibility of becoming angina-free was about 40% greater in the surgical than the medical group(**Stone et al.**, **2015**). Another study found that 80% of CABG patients were angina-free up to 5 years after surgery(**Fihn et al.**, **2001**).

Dyspnea following CABG was investigated. In a study in which 60% of patients experienced dyspnea before CABG, 54% of them were completely relieved of dyspnea, 22% reported some improvement, and 18% had no improvement 6 months following surgery. Nine percent of the total patients reported more dyspnea following surgery, with **>** 50% of them were dyspnea-free pre-surgery(**Caine et al.**, **1991**). Another study found that 71% of patients experienced dyspnea before surgery while 39% reported it 12 months post-surgery(**Hawkes et al.**, **2006**).

In a later study, 63% of CABG patients complained of dyspnea pre-surgery, with the proportion falling to 30% at 3 months and 33% at 12 months. The level of exertion at which these symptoms developed was also greater after surgery. Symptoms of chest pain and dyspnea were significantly reduced in both male and female patients following CABG. Thus in general, an improvement in angina and dyspnea has been observed following CABG(**Raja et al.**, **2012**).

**Allen**, **1990** investiated the exercise behavior at 6 and 24 months post-CABG. He found that 67% of patients became long-term regular exercizers by 2 years post-surgery. Thus physical functioning improves for some patients following CABG, while pre-operative inactivity continues or physical activity levels deteriorate following surgery for others.

**Herlitz et al.**, **1998** developed a physical activity score containing 6 questions for the self-estimation of physical abilities and limitations. The score improved over time, with the major improvement at 3 months, and further slight improvement at 2 years .

In contrast, others found no change, or decrease, in physical activity following CABG. One study found that 17% of previously active CABG patients reported decrease in leisure and social activities up to 2 years post surgery(**Serruys et al.**, **2005**).

Increased maximal exercise performance after CABG was reported. One study found that 6 months after CABG, daily physical activity increased, with reduction in number of days patients were unable to carry out usual activities, or confined to bed, due to their heart condition(**Phillips et al.**, **2007**).

**Firouzabadi et al.**, **2014** investigated of usual activity levels at home, at leisure, and socially, found that these were improved 1 year following surgery. Physical mobility was improved in 77% of patients 3 months after heart surgery.

Investigators in the coronary artery surgery study found that 68% of patients had a moderate activity level pre-surgery with no change in activity during the 5-year follow-up(**Jahangiry et al.**, **2017**).

1. **Adverse Effects:**

Some surgical complications and medical problems have resulted in hospitalization post CABG. In a study, 23% of CABG patients were re-hospitalized in first 6 months post surgery; 32% of them were due to cardiac problems. Complications of surgery (including cardiac complications) were responsible for 14% of gastrointestinal difficulties and for 9%, of other organ systems(**Montrief et al.**, **2018**).

In another study, 33% of CABG patients were re-hospitalized in the first 2 years post surgery, acute myocardial infarction, arrhythmia or angina were the most common reasons for re-admission. Risk factors for re-hospitalization were length of stay in ICU; severe non-cardiac complications; duration and severity of pre-operative cardiac symptoms; intra-aortic balloon insertion; pre-operative resting angina; female gender; age; diabetes; and surgical procedure (patients with left internal mammary artery graft or multiple arterial grafts are less likely to be re-hospitalized). Thus, there was a high rate of readmission post CABG, although this may denote that physicians hospitalize patients if there is a recent history of cardiac surgery(**Damgaard et al.**, **2005**).

The incidence of postoperative cerebrovascular accidents (CVA) after CABG ranges from 1.4% to 3.8%. Risk factors include age, previous stroke, diabetes mellitus, hypotension, hypertension, and female sex. Mortality rate is 10-fold higher among post-CABG patients with prior stroke with longer lengths of hospital stay(**Montrief et al.**, **2018**).

Although off-pump CABG was introduced to reduce adverse neurological complications, this was not proved. Postoperative delirium was about 10% post CABG, and was linked to functional decline at 1 month, short-term cognitive decline, and risk of late mortality, Risk factor for cognitive dysfunction after on-pump CABG include pre-existing cpgnitive impairment, cerebrocascular disease and central nervous system disorder. About 30% of CABG patients may have preoperative cognitive impairment(**Jensen et al.**, **2008**).

Nosocomial infections occur in 10% to 20% of cardiac surgery patients. Risk of deep sternal wound infection is increased in diabetics, obese patients (body mass index >30 kg/m2), and patients with COPD.

It is also increased with prolonged CPB time, prolonged intubation time, and surgical reexploration. To prevent surgical site infections in CABG patients, a multimodality perioperative approach is important. Infection rates may be improved by smoking cessation, optimizing nutritional status, tight glucose control, and weight loss(**Safaie et al.**, **2015**).

The more the transfusion of homologous blood, the more the risks of infection (especially sterna wound), myocardial depression, and both early and late death. In a retrospective analysis of 15.592 cardiovascular patients, the risk of sepsis and sternal wound infections increased with each unit of transfused blood. Also, in an RCT leukocyte-depleted blood had reduced rates of infection (17.9% versus 23.5%; *P* < 0.04) and 60-day mortality (7.8% versus 3.6%; *P* < 0.019)(**Surgenor et al.**, **2006**).

Incidence of acute renal failure (ARF) after CABG is 2% to 3% with 1% requiring dialysis. The risk factors are pre-existing renal dysfunction, decreased cardiac output, as in CHF or shock, insulin dependent diabetes, concomitant peripheral artery disease, advanced age, black race, female gender, and emergency surgical intervention or preoperative intraaortic balloon (**Thakar et al.**, **2004**).

Post-CABG myocardial dysfunction is common. Intraaortic balloon counterpulsation increases cardiac output and improve coronary blood flow. Patients with a left ventricular ejection fraction of <30% or with left main disease have a mortality benefit with the perioperative use of an IABP(**Montrief et al.**, **2018**). The PREVENT IV trial suggests that cardiac serum biomarkers for myonecrosis are elevated postoperatively even in about 10% of CABG subjects(**PREVENT IV Investigators\* et al.**, **2005**).

Moreover, both the short (30-day) and long-term (2-year) outcomes were worse in these patients, and this correlated with the degree of biomarker elevation(**Alexander et al.**, **2005**).

Postoperative AF is the most common post-CABG adverse events and occurs in 20-50% of patients. **Mariscalco et al** (**2008**), in an observational study of 1.878 patients undergoing CABG, found that post-CABG AF was associated with a 4-fold increase risk of disabling CVA and 3-fold increase risk of cardiac-related death. Risks which predispose to postoperative AF are peripheral artery disease, COPD, concomitant valvular heart disease, previous cardiac surgery, preoperative AF, pericarditis, male gender, and advanced age.

Postoperative AF occurs mostly within 5 days of surgery peaking on day 2. Multiple pharmacologic interventions were tried, but only perioperative beta blockade and amiodarone were effective in reducing AF. Isolated post-CABG AF usually resolves spontaneously within 6 weeks postoperatively. So, rate control with beta blockers or conversion with amiodarone is the first line of treatment. Postoperative anticoagulation may be used in rate controlled patients(**Halonen et al.**, **2006**).

Chapter II: Cardiac Dysfunction in the CABG Patient

Over the past decade, there has been a significant decline in cardiac surgery–associated mortality, despite an increase in procedural complexity. Although the average perioperative mortality currently is 1% to 2%, the rate of major cardiovascular complications remains high. Low-cardiac-output syndrome (LCOS) is the most common and the most serious complication and is associated with increased morbidity, short- and long-term mortality, and healthcare resource utilization. Other cardiac complications include heart failure, left ventricular dysfunction, and myocardial infarction (1).

1. **Low Cardiac Output Syndrome:**

Low-cardiac-output syndrome (LCOS) is the most common and the most serious complication and is associated with increased morbidity, short- and long-term mortality, and healthcare resource utilization. This syndrome is characterized by decreased heart pump function, leading to reduced oxygen delivery (DO2) and subsequent tissue hypoxia. The most common definition of LCOS also includes decreases in the cardiac index (CI) to<2.0 L/min/m2 and a systolic blood pressure of<90 mmHg, in conjunction with signs of tissue hypoperfusion (cold periphery, clammy skin, confusion, oliguria, elevated lactate level) in the absence of hypovolemia (2).

1. ***Risk Factors and Predictors***

To date, several risk factors and predictors have been recognized (**[Table 1](https://www.jcvaonline.com/article/S1053-0770(16)30151-3/fulltext" \l "t0005)**). Furthermore, a number of outcome prediction models have been developed, including the commonly used EuroSCORE, which predicts perioperative cardiovascular alterations. Independent significant risk factors for LCOS, including advanced age (>65 years), impaired LV function (<40%), on-pump coronary artery bypass grafting (CABG), emergency surgery or cardiopulmonary bypass (CPB), and incomplete revascularization, have been described. Diabetes mellitus and preoperative renal dysfunction are not separate predictors, but in combination they increase the risk of LCOS by 50% (3).

Importantly, there have been changes in the recognized risk factors over time. Thus, during the last 20 years, common risk factors such as hypertension, being female, triple-vessel disease, and left main vessel disease are no longer statistically significant, whereas the risk associated with low preoperative ejection fraction has doubled. Another risk factor is malnutrition, which is associated with a 2-fold increase in the probability of postoperative inotropic support and independently predicts adverse clinical outcomes (3).

**Table 1: Predictors and Risk Factors of Postoperative LCOS**

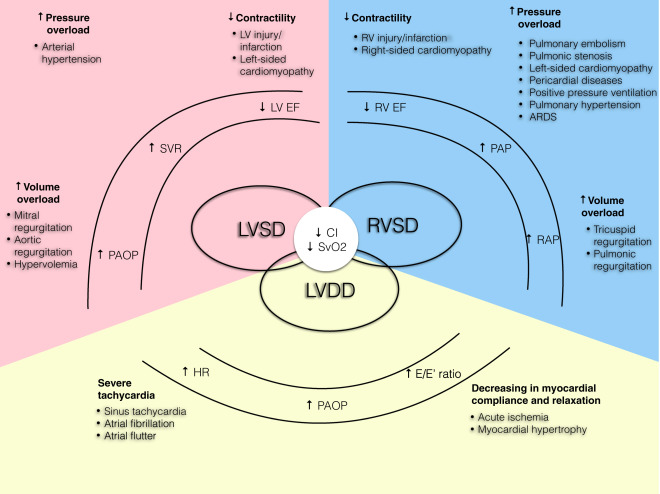
|  |  |
| --- | --- |
| **Type** | **Risk Factors** |
| **Preoperative factors** | Age>65 years |
|  | LVEF<40% |
|  | On-pump CABG |
|  | DM and CKD |
|  | Malnutrition |
| **Intraoperative factors** | CPB duration |
|  | Emergency surgery |
|  | Incomplete revascularization |
| **Laboratory predictors** | Hemoglobin |
|  | TLC<2,000 cells per microliter |
|  | NT-proBNP |
| **BNP** |
|  | hFABP |

Abbreviations: BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CPB, coronary artery bypass; DM, diabetes mellitus; hFABP, heart fatty acid binding protein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; TLC, total lymphocyte count.

1. ***Pathophysiology***

Most interventions that include CPB with cardioplegic arrest lead to myocardial dysfunction, which typically results from ischemic/reperfusion injury of the heart. The persistence of such dysfunctions may vary from temporary (up to 24 hours), for stunning, to persistent, in cases of profound ischemia and myocardial infarction. The contributing factors include preoperative myocardial dysfunction, degree of myocardial protection, systemic inflammatory responses, and alterations in signal transduction systems (4).

The following pathophysiologic mechanisms of LCOS should be highlighted: (1) LV systolic dysfunction, (2) right ventricular (RV) systolic dysfunction, and (3) diastolic dysfunction, also called heart failure with preserved ejection fraction ([**Fig 1**](https://els-jbs-prod-cdn.literatumonline.com/cms/attachment/2087803129/2074682855/gr1.jpg)) ( [**Lomivorotov**](https://www.semanticscholar.org/author/Vladimir-Vladimirovich-Lomivorotov/4559510) **et al 2017 )**. The forementioned mechanisms may occur in isolation or in combination. Conditions such as valvular heart disease, pulmonary hypertension, mechanical valve dysfunction, and respiratory failure, also contribute to LCOS development (4).



**Figure 1: A schematic presentation of the pathophysiology of postoperative LCOS. The most common causes and typical signs are presented. The specific clinical scenario usually is associated with particular pathophysiologic type of LCOS. However, in clinical practice, a combination of different pathophysiologic pathways often leads to the development of postoperative LCOS. ARDS, acute respiratory distress syndrome; CI, cardiac index; E, early flow velocity at the level of the mitral valve; E′, early velocity of the mitral annulus (myocardial Doppler imaging); EF, ejection fraction; HR, heart rate; LVDD, left ventricular diastolic dysfunction; LV, left ventricle; LVSD, left ventricular systolic dysfunction; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; RAP, right atrial pressure; RV, right ventricle; RVSD, right ventricular systolic dysfunction; SVR, systemic vascular resistance; SvO2, mixed venous oxygen saturation.**

***LV Systolic Dysfunction***

LV function is derivative of preload, afterload, and contractility; LV systolic dysfunction occurs due to loss of functional myocytes or a decrease in their function. In most cases, the loss of functional myocytes develops as a result of necrosis due to impaired coronary circulation and ischemia/reperfusion injury or the less-understood phenomenon of apoptosis. A loss of function of vital myocytes commonly is transient during stunning or may be refractory to reversal with conditions such as infection; tachycardia; cardiac valvular disease; metabolic abnormality (acidosis, hypoglycemia, hypocalcemia); exposure to cardiac toxins; idiopathic dilated cardiomyopathy; and genetic disorders (familial dilated cardiomyopathy, hypertrophic cardiomyopathy, muscular dystrophies). The impairment of cardiac response to preload leads to dramatic decreases in cardiac output (CO) and oxygen delivery to other organs, increased left atrial pressure and capillary wedge pressure, and cardiogenic pulmonary edema. Although the LV usually works against relatively high systemic arterial pressure, the significant afterload increase also may induce LV systolic dysfunction (5).

***LV Diastolic Dysfunction***

LCOS sometimes is associated with preserved LV systolic function (ejection fraction). In such cases, the contractile function of the myocardium is diminished, despite preserved global systolic performance. These conditions result from the inability of the ventricular chamber to accept an adequate volume of blood, despite normal preload, and present as diastolic dysfunction. However, diastolic dysfunction may be accompanied by either impaired or preserved ejection fraction. From a pathophysiologic perspective, diastolic dysfunction is characterized by abnormal relaxation and filling of the LV during the diastolic phase of the cardiac cycle that may be caused by the following mechanisms: (1) severe tachycardia (upon atrial fibrillation), (2) decreased myocardial compliance, and (3) impaired ventricular relaxation. The processes intimately involved in the development of diastolic dysfunction, at the cardiomyocyte level, relate to calcium removal from the cytosol and calcium homeostasis, the adequacy of cross-bridge detachment, and intrinsic functional cytoskeletal element disorders (6).

Diastolic dysfunction is a widespread phenomenon, occurring in up to 70% of cardiac patients postoperatively. Despite its high prevalence, diastolic dysfunction alone often is insufficient to induce the development of acute heart failure; however, in combination with other predisposing factors, such as atrial fibrillation, impaired coronary perfusion, and arterial hypertension, it may lead to decompensation. Diastolic dysfunction therefore is believed to be an early sign of myocardial ischemia (7).

The close relationship between the systolic and diastolic functions of the LV should be acknowledged. Thus, inotropic catecholamine stimulation affects both systole and diastole and may enhance diastolic dysfunction, whereas reduced LVEF leads to increased end-systolic volume and prolongs the diastolic phase of the cardiac cycle (8).

***Right Ventricular Dysfunction***

The principal pathophysiologic mechanisms of RV dysfunction include increased RV preload, increased RV afterload, impaired right coronary artery perfusion, and decreased contractility. The specific features of RV perfusion and their alterations during increased pulmonary artery pressure are important to understand. Physiologically, perfusion of the right coronary artery, in contrast to the left coronary artery, occurs during both diastole and systole. Under conditions of pulmonary hypertension, the RV pressure increases and leads to decreased right coronary artery perfusion, explaining why diastolic arterial pressure maintenance is highly important for providing optimal left and right coronary blood flow (9).

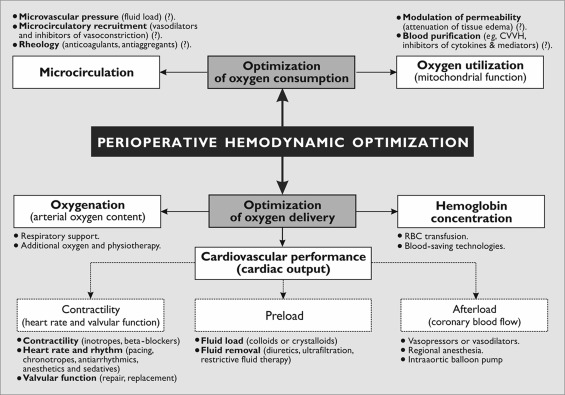
In postoperative settings, RV dysfunction often develops due to a combination of mechanisms. Thus, cardiac patients encounter many conditions associated with RV failure. Perioperative RV ischemia and infarction are major causes of contractility impairment. Tricuspid or pulmonic regurgitation leads to excessive volume preload, whereas left-sided valvular disease or cardiomyopathy, pulmonary hypertension or embolism, acute respiratory distress syndrome, and high positive-pressure ventilation are common causes of pressure overload. Taking into account that the RV normally provides low-pressure perfusion of the pulmonary vasculature, it is highly sensitive to even moderate pulmonary artery pressure increases. RV failure may develop due to pulmonary hypertension or contractile impairment associated with a rapid progression of RV dilation, resulting in a rise in end-diastolic RV pressure. These alterations lead to an interventricular septum shift toward the already underfilled LV chamber, reducing LV preload and decreasing CO (10).

1. ***Hemodynamic Monitoring and Directed Therapy***

The goal of perioperative hemodynamic management in cardiac surgery should be optimization of the balance between DO2 and oxygen consumption (VO2); this is especially important in patients with low CO. The individualized choice of perioperative monitoring technique depends on the type of surgery and the patient-related risk. Over time, a number of new hemodynamic monitoring methods have appeared, including real-time measurements and less-invasive approaches (11).

***Goal-Directed Hemodynamic Therapy in Cardiac Surgery***

Potential therapeutic interventions for the optimization of hemodynamics and oxygen transport are shown in [**Figure 2**](https://els-jbs-prod-cdn.literatumonline.com/cms/attachment/2087803129/2074682856/gr2.jpg)**.** ( [**Lomivorotov**](https://www.semanticscholar.org/author/Vladimir-Vladimirovich-Lomivorotov/4559510) **et al 2017 )**. In cardiac surgery, hypoperfusion, CO reduction, and decreased DO2 may result from surgical manipulations on the heart, arrhythmias, impaired preload and vascular tone, myocardial depression, and valve dysfunction. Perioperative goal-directed therapy (GDT), guided by invasive hemodynamic monitoring and ultrasound methods, aims to counteract these pathophysiologic changes and to prevent LCOS (12).



**Figure 2: The strategy for perioperative hemodynamic optimization. CVVH, continuous veno-venous hemofiltration; RBC, red blood cell**

Although PAC use still is recommended for guiding therapy in high-risk cardiac surgeries (eg, CS, decreased ejection fraction, IABP use, redo surgery, pulmonary hypertension), in low-risk coronary and vascular patients, the maintenance of a “supranormal” stroke volume index (SVI), CI, and DO2 using either the PAC or lithium dilution techniques did not improve clinical outcomes. Esophageal Doppler has been used to evaluate the concept of postoperative, nurse-directed circulatory status optimization to maintain an SVI>35 mL/m2 and to shorten the duration of post–cardiac surgery hospitalization. Using a combination of PAC-derived (CI and SVI) and metabolic (mixed venous oxygen saturation and lactate) targets, Pölönen et al have shown that GDT after cardiac surgery was accompanied by more frequent administration of fluids and inotropes and resulted in shorter hospitalizations and decreased morbidity (13).

Several other recent cardiac surgery studies have demonstrated the advantages of early hemodynamic optimization when GDT starts immediately after anesthesia induction. In one study, patients with a EuroSCORE>3 underwent on-pump CABG; the GDT group was managed with pulse-contour-based technology (FloTrac, Edwards Lifesciences) and central venous oximetry to maintain target CI, SVI, systemic vascular resistance, DO2, SCVO2, and SVV values. Compared with the control group, the GDT group received more fluids and more adjustments to their inotropic agents. Importantly, this group of patients demonstrated shorter periods of mechanical ventilation, shorter inotrope therapy duration, and reduced ICU and hospital stays (14).

The outcome benefit of hemodynamic GDT might be even more evident in high-risk patients when it aims to both prevent and treat low CO. This has been confirmed in several recent studies. In a randomized study by Goepfert et al patients undergoing CABG and/or aortic valve replacement who received early GDT, including maintenance of a CI>2 L/min/m2, SVV<10%, and optimized GEDV, had fewer complications and decreased lengths of postsurgical ICU stays. In complex elective valve surgery, GDT based on transpulmonary thermodilution and oxygen transport parameters led to increased volumes of fluid therapy, improved hemodynamics and DO2, and required shorter periods of respiratory support compared with patients treated using a PAC-guided algorithm (16).

1. ***LCOS Prevention***

LCOS represents a major cardiac surgery challenge because it is associated with increased morbidity and mortality. The efforts of the surgical team aim to reduce the LCOS burden, especially in high-risk patients. Hence, the early use of numerous drugs and techniques is intended to reduce the incidence and severity of this complication (17).

***Cardioplegia Types***

Since its introduction into clinical practice, cardioplegia has become a gold standard in the management of patients undergoing CPB during cardiac surgeryTo date, the majority of studies have compared the effects of cold crystalloid cardioplegia and cold blood cardioplegia on morbidity and mortality. A recent meta-analysis by **Zeng et al** examined 2,866 patients from 12 randomized controlled studies to compare the effects of these cardioplegia techniques. Although cold blood cardioplegia was observed to reduce the incidence of perioperative myocardial infarction compared with cold crystalloid cardioplegia, no differences in the overall incidences of spontaneous sinus rhythm, 30-day mortality, atrial fibrillation, or stroke were observed (18).

The data regarding the clinical efficacy and safety of warm versus cold blood cardioplegia are controversial**. Mallidi et al,** in a large retrospective study of 6,064 patients undergoing isolated CABG, demonstrated that warm or tepid blood cardioplegia may be associated with better early and late event-free survivals than cold cardioplegia. Conversely, the earliest study by **Martin et al** demonstrated that warm blood cardioplegia was associated with increased rates of neurologic events (warm, 4.5%; cold, 1.4%; p<0.005) and perioperative stroke (warm, 3.1%; cold, 1.0%; p<0.02) compared with crystalloid cardioplegia. However, the rate of postoperative mortality, Q-wave infarction, and IABP did not differ between the 2 groups (19, 20).

Standard diluted blood cardioplegia can be modified to undiluted blood cardioplegia (microplegia) to retain many of the advantages, without the potential disadvantages, of hemodilution and leads to reduced rates of postoperative LCOS The beneficial effects of microplegia might be explained by the reduced myocardial edema associated with the smaller volume of cardioplegia required (20).

***Volatile Anesthetics***

Volatile halogenated anesthetics are used widely worldwide for anesthetic management of cardiac procedures. According to the CABG guidelines from the American College of Cardiology Foundation and the American Heart Association, volatile anesthesia can be useful in reducing the risk of perioperative myocardial ischemia and infarction (class of recommendations: IIa; Level of Evidence: A). A meta-analysis of 22 studies involving 1,922 patients showed that a halogenated anesthetic regimen was associated with improved outcomes after cardiac surgery. Specifically, volatile anesthetics were associated with significant reductions in the incidence of myocardial infarctions and mortality. Moreover, the need for inotropic support also was reduced significantly in the volatile anesthetic group (21).

***Intra-aortic Balloon Pump***

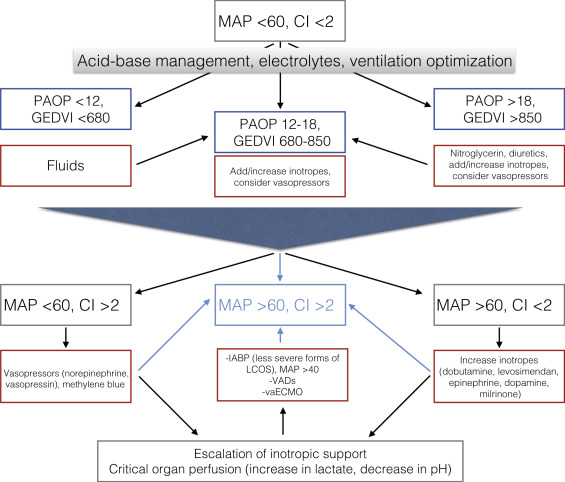
There still is debate regarding whether prophylactic IABP use can improve cardiac surgery outcomes. One single-center, prospective, randomized controlled trial in patients with poor (<35%) LVEF and no hemodynamic instability assessed the influence of preincision IABP use on clinical outcomes. There were no differences in the major morbidity rate (40% in the IABP group and 31% in the control group; odds ratio, 1.49 [95% confidence interval, 0.68-3.33]) or in the observed preoperative and postoperative CIs. Fewer patients in the IABP group (24%) than in the control group (44%) required dopamine infusion (p = 0.043) (22).

***Triiodothyronine***

In the cardiovascular system, triiodothyronine is responsible for regulating CO and blood pressure. Cardiac surgery, with or without CPB, induces a marked and persistent depression in circulating thyroid hormone levels during the postoperative period in both adults and children. Furthermore, a low baseline triiodothyronine level is a strong predictor of LCOS and death in CABG patients. As a result, numerous trials have been conducted to assess the influence of perioperative triiodothyronine supplementation on cardiac surgery outcomes, with conflicting results. In a double-blind, randomized, placebo-controlled study of 170 patients undergoing CABG surgery, Mullis-Jansson et al compared the effects of prophylactic intravenous triiodothyronine, administered after removal of the aortic cross-clamp, versus placebo on patient hemodynamic profiles and inotrope requirements. Patients who received triiodothyronine had higher CI and lower inotrope requirements after surgery. Moreover, 7 patients in the placebo group required postoperative mechanical assistance compared with none in the triiodothyronine group (p = 0.01) (23).

1. ***Treatment of LCOS***

Treatment of LCOS is complex and is intended to increase tissue DO2 and prevent worsening organ dysfunction and failure by providing adequate hemodynamic support ([**Fig 3**](https://els-jbs-prod-cdn.literatumonline.com/cms/attachment/2087803129/2074682858/gr4.jpg)). If identified, the cause (eg, graft dysfunction, valvular incompetence, pericardial tamponade, residual defects) must be corrected rapidly. The first line of LCOS therapy, to be initiated as soon as the volume status is optimized, is the use of inotropes and vasodilators to improve contractility, preload, and afterload. Nevertheless, inotropic agents, which are used primarily in patients with LCOS, also can improve CO, but they achieve this goal at the expense of increased myocardial consumption and an increased mortality risk. Maintenance of acid-base balance and normothermia, correction of electrolyte abnormalities, and ventilation management ameliorate the results of LCOS treatment and improve responsiveness to catecholamines. The properties of commonly used inotropes and vasopressors are summarized in **[Table 2](https://www.jcvaonline.com/article/S1053-0770(16)30151-3/fulltext" \l "t0015) (24).** ( [**Lomivorotov**](https://www.semanticscholar.org/author/Vladimir-Vladimirovich-Lomivorotov/4559510) **et al 2017 )**.



**Figure 3: LCOS treatment algorithm based on measures of preload (PAOP) and/or heart volumes (GEDVI). CI, cardiac index; venoarterial ECMO, extracorporeal membrane oxygenation; GEDVI, global end-diastolic volume index; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; VAD, ventricular assist device.**

**Table 2: Drugs Used for the Treatment of LCOS** ( [**Lomivorotov**](https://www.semanticscholar.org/author/Vladimir-Vladimirovich-Lomivorotov/4559510) **et al 2017 )**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Intervention | Indications | Dosages | Receptors and Effects | Side Effects |
| Dobutamine | LCOS treatment | 1-20 µg/kg/min | β-adrenergic, ↑inotropy | Arrhythmia (less than dopamine) |
| Dopamine | LCOS treatment | 0.5-2 µg/kg/min | DA, vasodilation | Worsens renal injury in states of LCOS |
| **2-5 µg/kg/min** | β-adrenergic, ↑inotropy | Tachycardia |
| **5-20 µg/kg/min** | α- and β-adrenergic, vasoconstriction, ↑inotropy | Arrhythmia, tachycardia |
| Epinephrine | LCOS treatment, anaphylaxis | 0.01-0.03 µg/kg/min | β-adrenergic, ↑inotropy | Lactic acidosis, hyperglycemia, mesenteric ischemia |
| **0.03-0.1 µg/kg/min** | α- and β-adrenergic, vasoconstriction, ↑inotropy |
| Norepinephrine | Decreased SVR, vasoplegic syndrome, septic shock | 0.01-0.1 µg/kg/min | α- and β-adrenergic, vasoconstriction, ↑inotropy (less pronounced) | Arrhythmia, tachycardia |
| Vasopressin | Decreased SVR, vasoplegic syndrome | 0.01-0.1 IU/min | V1 stimulation, vasoconstriction | Myocardial ischemia, ventricular arrhythmia |
| Milrinone | LCOS treatment | 0.5-1 µg/kg/min | Phosphodiesterase inhibitor, ↑inotropy, vasodilation | Thrombocytopenia, arrhytmia, tachycardia |
| Levosimendan | LCOS treatment and prophylaxis | 10 µg/kg loading dose, 0.1 µg/kg/min infusion | Increasing myofilament sensitivity to calcium | Arrhythmia, hypotension |

Abbreviations: DA, dopaminergic receptor; LCOS, low-cardiac-output syndrome; SVR, systemic vascular resistance; V1, vasopressin-1 receptor.

1. ***Catecholamines***

***Dopamine***

Dopamine demonstrates dose-dependent pharmacodynamics. Inappropriate dosing of dopamine is relatively common due to the significant interindividual variability of dopamine-receptor sensitivity, metabolism, and distribution (25).

Sinus tachycardia and arrhythmia are the most common side effects of dopamine treatment. These chronotropic effects may be deleterious for patients with ischemic heart disease and may aggravate injured and hibernating myocardium, despite causing an initial CO improvement. Another unwanted effect of dopamine is the inhibition of the peripheral chemoreceptors of carotid bodies. Peripheral chemoreceptors are essential for abrupt ventilatory and arterial pressure responses to hypoxia, hypercapnia, and acid-base disturbances. Dopamine has been shown to depress ventilation, reduce oxygen saturation, prolong apnea, and provoke ventilation/perfusion mismatching Thus, despite a theoretical background of favorable low-dose dopamine effects on renal function (presynaptic type 1 and postsynaptic type 2 dopaminergic-receptor agonism), clear evidence exists against its routine use for this purpose. Furthermore, dopamine worsened renal injury in cardiac patients, despite an increase in blood flow (26).

***Dobutamine***

The principal action of dobutamine is on β1-adrenergic receptors, with lesser stimulation of β2- and α-adrenergic receptors. This drug predominantly enhances ventricular contraction and slightly affects vascular tone. It also increases contractility, stroke volume, and CO. Dobutamine also decreases pulmonary and systemic vascular resistance without significantly increasing HR or the risk of other adverse effects when administered to patients with proper hemodynamic status (avoid hypovolemia) and at a correct initial rate of infusion (avoid boluses). Properly administered dobutamine improves myocardial metabolism, despite increasing myocardial VO2. This favorable effect is associated with increased DO2 and coronary blood flow due to an improved coronary perfusion pressure, perfusion time, and direct vasodilation of the coronary arteries. These properties make dobutamine attractive for use in patients with LCOS associated with postoperative myocardial stunning or hibernation (27).

***Norepinephrine***

Norepinephrine is predominantly an α-adrenergic agonist with modest effects on β-adrenergic receptors. It has a wide therapeutic range, which presumably is a result of the downregulation of α-adrenergic receptors during critical illness. Thus, successful treatment with doses ranging from 0.01-to-5 µg/kg/min have been reported for patients experiencing sepsis. As for any catecholamine, volume repletion is the principal condition for safe administration. Norepinephrine treatment of hypotensive, normovolemic patients experiencing shock resulted in better hemodynamic and oxygenation profiles than that achieved with dopamineand increased both urine output and creatinine clearance. For chronically volume-depleted individuals, such as those undergoing prolonged diuretic treatment for congestive heart failure, norepinephrine should be administered with caution due to the risk of renal dysfunction and nonocclusive mesenteric ischemia (28).

***Epinephrine***

Epinephrine is a nonselective adrenergic agonist with high affinity for β1-, β2-, and α-adrenoreceptors. Due to its unpredictable inotropic and vasoconstrictive properties, detrimental effects on splanchnic blood flow and ability to induce lactic acidosis, epinephrine is not a first-line drug for LCOS treatment, by some clinicians, but is used occasionally in the most severe cases of LCOS that are resistant to conventional inotropic therapy. Epinephrine, a potent vasoconstrictor (α1-agonism) agent with remarkable inotropic and chronotropic effects (β1-agonism) and the capacity to decrease the release of inflammatory mediators from mast cells and basophils (β2-agonism), is the drug of choice after cardiac arrest and anaphylaxis (29).

***Phenylephrine***

As an α1-adrenergic agonist, phenylephrine increases systemic vascular resistance, without affecting CO, with doses of 0.5-to-10 µg/kg/min. Compared with norepinephrine, prolonged infusion of phenylephrine was associated with decreased DO2 and splanchnic blood flow. This drug commonly is used for the effective management of transient arterial hypotension induced by general anesthesia but cannot be recommended for LCOS management. Vasopressin and methylene blue are other drugs that can be used for restoring MAP in conditions associated with low systemic vascular resistance after CPB (vasoplegic syndrome) (30).

1. **Phosphodiesterase Inhibitors**

Milrinone, amrinone, and enoximone increase intracellular cyclic adenosine monophosphate by inhibiting phosphodiesterase type III (PDE III) and producing inotropic, systemic, and pulmonary vasodilatory effects. Milrinone does not increase myocardial VO2 or HR, unlike catecholamines. Despite their favorable hemodynamic effects, there is abundant evidence that PDE III inhibitors worsen long-term clinical outcomes in patients with acute and chronic heart failure. Concerns about the trend toward increased mortality associated with milrinone use in cardiac surgery patients were published in 2 recent meta-analyses. Such results may be explained, at least in part, by the increased incidence of new-onset postoperative atrial fibrillation after cardiac surgery, associated with intravenous milrinone (31).

Milrinone most commonly is used as a second-line agent when hemodynamic improvement cannot be achieved with dobutamine and is especially effective in patients with RV systolic dysfunction due to its vasodilatory effects on pulmonary vessels, leading to a decreased RV afterload. Administration of inhaled (aerosolized) milrinone also effectively decreased pulmonary hypertension and avoided adverse systemic hemodynamic effects. Gaseous nitric oxide and aerosolized prostacyclin (epoprostenol) are other pulmonary vasodilators used in the treatment of pulmonary hypertension (31).

1. **Levosimendan**

Levosimendan is a relatively new drug that was approved initially for the management of decompensated heart failure. In the next chapter, we discussed in details the role of Levosimendan in post-CABG cardiac dysfunction.

1. **Glucose-Insulin-Potassium Infusion**

According to the available data, glucose-insulin-potassium (GIK) infusions can be used as adjunctive therapy to treat postsurgical LCOS without serious adverse events. Szabó et al reported the results from a retrospective, observational study involving 89 patients treated with high-dose GIK after cardiac surgery. In the majority of patients (69.7%), GIK was used to treat postoperative cardiac failure. The authors concluded that the high-dose GIK regimen allowed for substantial amounts of glucose to be infused into both diabetic and critically ill patients while maintaining acceptable blood glucose control. Furthermore, a case series examined metabolic support using glutamate and high-dose GIK in 16 patients for whom IABP placement was considered after unsuccessful weaning from CPB. Rapid improvement in hemodynamic performance was seen within the first hour, with almost full recovery within 6 hours in the surviving patients (32).

1. ***Short-Term Mechanical Circulatory Support***

The timing of IABP placement in patients who develop LCOS after cardiac surgery plays a pivotal role in survival. Compared with postoperative IABP insertion, intraoperative insertion resulted in a mortality reduction from 64.4% to 41.5% (p<0.001) in a case series involving 1,051 patients. Aside from having beneficial effects on coronary perfusion, IABP therapy also improved global and regional splanchnic oxygenation in patients with LCOS after cardiac surgery (33).

Extracorporeal membrane oxygenation (ECMO) is one of the earliest and most widely used mechanical circulatory support systems for the nonpharmacologic treatment of CS. The cardiac indications for ECMO include failure to wean from CPB, life-threatening heart failure secondary to myocardial infarction or fulminant myocarditis, and the need for an adjuvant to conventional cardiopulmonary resuscitation (34).

Several ventricular assist devices that provide short-term hemodynamic support are available, including the 3 described below. Each of these devices is capable of reducing LV load and improving tissue perfusion (35).

1. **Heart Failure:**

Prolongation n patients with heart failure due to ischemic cardiomyopathy (ejection fraction less than 35%), STICH trial showed there is no long-term benefit of CABG over medical therapy. Surgical ventricular reconstruction (SVR) showed no improvement when compared with CABG alone in patients with heart failure. However, inadequate reduction of LV volume in STICH SVR arm was criticized and observational study has shown better outcome in patients with low left ventricular end systolic volume less than 60 mL/m 2 after SVR. Modified SVR technique termed overlapping left ventriculoplasty (OLVP) and mitral valve repair have still not been tested rigorously in large RCT (36).

Perioperative myocardial injury, pre-existing left ventricular systolic dysfunction (LVSD) and stunning due to reperfusion injury all can contribute to heart failure after CABG. Cardiac biomarkers can help in early diagnosis of post CABG heart failure. Increased BNP just after surgery are significantly associated with more frequent in-hospital adverse cardiovascular events, longer hospital stays, increased incidence of major adverse cardiovascular events and all-cause mortality after discharge as well as poor long-term physical function (37).

Reperfusion injury after CABG is different from post MI reperfusion injury and manifest clinically as arrhythmia, stunning, cardiac failure and MI. Reperfusion injury is characterized by myocyte loss beyond that owing to ischemia and is probably due to apoptosis. Myocardial stunning in the post CABG patient is manifested by low output requiring positive inotropic agents in an otherwise uneventful surgery. Although there is controversy about the dominant cause for post CABG elevation of cardiac biomarkers three large clinical trials have shown reperfusion injury due to sub optimal myocardial protection is the leading cause for myonecrosis (38).

Changing the cardioplegic solution and ischemic preconditioning by cross clamping the aorta for few minutes and then releasing it has been used experimentally in the operation theatre to reduce reperfusion injury. Some volatile anesthetics and opioids have been also shown experimentally to reduce reperfusion injury. However, experimental therapies to decrease reperfusion injury after CABG such as increasing tissue adenosine (acadesine), preventing and increase in cytosolic calcium (cariporide) and a complement inhibitor (pexelizumab) has failed in the Phase 3 stage of the clinical trials (39).

In an observational setting stunning results were generated by a Swedish group providing complex metabolic protection during CABG surgery. Their intervention includes minimizing inotropes and using mechanical assist device, minimizing after load and hemodynamic monitoring with urine output and mixed venous oxygen saturation level and metabolic support with high dose glutamate and glucose–insulin–potassium (GIK). Heparin which stimulates free fatty acid release was neutralized with protamine. In a randomized controlled study GIK infusion to produce normoglycemia significantly reduced troponin levels and improved echocardiographic findings of heart function. The infusion was given from the beginning of CABG surgery till 24 h after (40).

IABP is a well-established treatment in low output states after CABG. However, recent Cochrane review shows potential benefit of IABP in high risk patients before CABG. Augmentation with IABP for 1 h was deemed sufficient. Implantable cardioverter defibrillators (ICD) after CABG have mortality benefit in patients with LVSD (EF less than 30–40%). Although there are no randomized controlled trials directly addressing post-CABG population, most of the well-known primary prevention trials had large proportion of (45–57%) patients who have undergone CABG. Inducible or nonsustained VT and broad QRS complexes (more than 120 ms) are indicators for ICD in addition to symptoms and ejection fraction. The consensus opinion is to wait for 3 months before evaluating for ICD. Addition of cardiac resynchronization therapy to ICD and optimal medical therapy reduced death and hospitalization owing to heart failure in patients with NYHA class II or III heart failure, a wide QRS complexes and LVSD. In this trial around 35% of patients in both arms had undergone CABG (41).

Remote ischemic preconditioning ‘describes the cardioprotection elicited from applying brief episodes of nonlethal ischemia and reperfusion to an organ or tissue distant or remote from the heart before a period of sustained myocardial ischemia’. This is a novel low cost almost noninvasive method for protection of the myocardium from reperfusion injury (42).

1. **Outcomes of CABG in patients with left ventricular dysfunction:**

Patients with reduced EF (< 30%) undergoing CABG have been consistently shown in the literature to have higher operative mortality and reduced long-term survival compared with patients with preserved EF. However, 30-day mortality has significantly improved over time, passing from a 20% in the late 1980s to a 5% in patients operated on after 2000. This enhancement in operative outcome is certainly multifactorial and probably related to improvements in myocardial protection strategies and perioperative management of related comorbidity (43).

**Kunadian,** in a meta-analysis including 4119 patients from 26 observational studies with ischemic LVD (mean preoperative EF = 24%) undergoing CABG, reported a mean estimated 30-day mortality of 5.4%, with a limited postoperative use of IABP (8%) and inotropic support (43%); a significant improvement in postoperative systolic function, as mean EF improved from 24 to 35%; a mean estimated 5-year survival rate of 75%. These results demonstrated that CABG can be performed in this subgroup of patients with acceptable operative mortality and long-term survival. The comparison between medical therapy and CABG in the treatment of chronic stable angina has been addressed in several early trials (44).

Chapter III: Use of Levosimendan in Cardiac Surgery

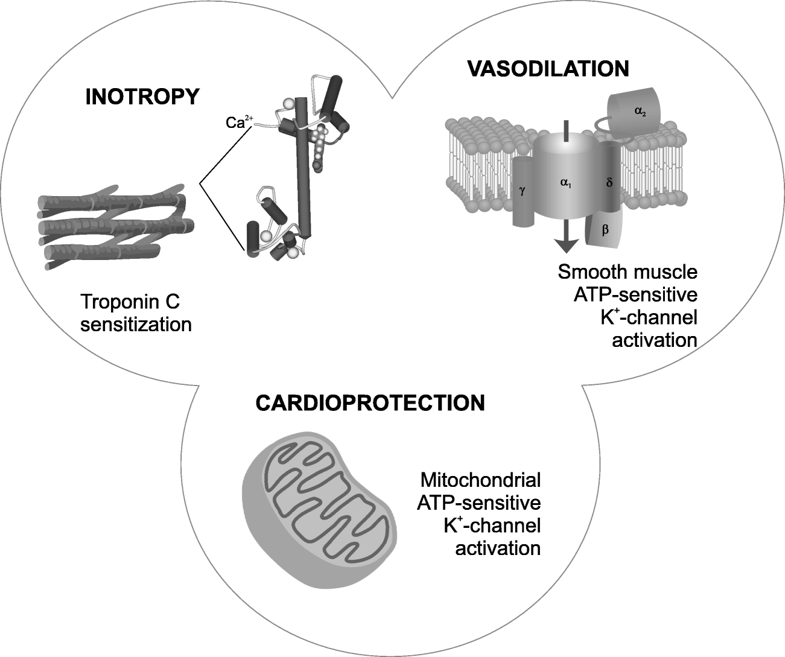
Levosimendan has been in clinical use for 15 years. In addition to its original indication for acutely decompensated heart failure, it has also been used to stabilize patients undergoing cardiac surgery. Abundant literature from exploratory studies supports the rationale for its use in this indication, and this is also supported by its benign effect on kidney function (1).

1. **Mechanisms of Action of Levosimendan:**

Levosimendan is an inotropic drug that has three major mechanisms of action: positive inotropy, vasodilation, and cardiac cytoprotection. The first major mechanism of action of levosimendan is its interaction with cardiac troponin C to form the basis of its Ca2+-sensitizing mechanism. The binding of the drug to troponin C increases the sensitivity of troponin C fibers to ionic free calcium, which in turn helps protract the molecular interaction between troponin C and troponin I, thus increasing cardiac contractility without increasing ionic free calcium. This is a distinctive feature of levosimendan compared with all other inotropic agents, which increase the concentration of ionic free calcium in cardiomyocytes, exposing them to lethal concentrations of ionic calcium. Elevated intracellular ionic calcium has been associated with cardiac remodeling, arrhythmia, and increase in oxygen consumption. Even with its direct effects of increasing myocardial contractility and enhancing rapid ventricular filling, levosimendan does not affect left ventricular relaxation (2).

The second mechanism of action of levosimendan is its vasodilatory properties. The drug is capable of opening ATP-dependent potassium channels in vascular smooth muscles, which results in dilatation of arteries in coronary, peripheral, and pulmonary circulation while causing venodilation of the portal and saphenous systems, thus causing a reduction in right ventricular preload and afterload (2).

The third mechanism of action of the drug is its cytoprotective properties. Experimental studies have suggested that levosimendan’s ability to open cardiac mitochondrial ATP-sensitive K+ channels can reduce production of free radicals within the cells. This in turn provides protection against stressful conditions to the cell and reduces cell destruction and stimulation of production of inflammatory response markers. Cardioprotection during acute and chronic heart failure via reduction in myocardial inflammation, remodeling, ischemia-reperfusion injury, and myocyte apoptosis has also been recognized with the use of levosimendan and/or its active metabolite OR1896. This effect was not only observed in myocardial cells but also in brain cells (3).



**Figure 4: mechanisms of action of levosimendan ( [Bouchez](https://link.springer.com/article/10.1007/s10557-018-6838-2" \l "auth-1) et al., 2018 ).**

1. **Pharmacokinetic:**

The pharmacokinetics of levosimendan are linear at the therapeutic dose range of 0.05-0.2 microg/kg/minute. The short half-life (about 1 hour) of the parent drug, levosimendan, enables fast onset of drug action, although the effects are long-lasting due to the active metabolite OR-1896, which has an elimination half-life of 70-80 hours in patients with heart failure (New York Heart Association functional class III-IV). Although levosimendan is administered intravenously, it is excreted into the small intestine and reduced by intestinal bacteria to an amino phenolpyridazinone metabolite (OR-1855). This metabolite is further metabolised by acetylation to N-acetylated conjugate (OR-1896). The circulating metabolites OR-1855 and OR-1896 are formed slowly, and their maximum concentrations are seen on average 2 days after stopping a 24-hour infusion. The haemodynamic effects after levosimendan seem to be similar between fast and slow acetylators despite the fact that the enzyme N-acetyltransferase-2, which is responsible for the metabolism of OR-1855 to OR-1896, is polymorphically distributed in the population. Levosimendan reduces peripheral vascular resistance and has direct contractility-enhancing effects on the failing left ventricle. It also improves indices of diastolic function and seems to improve the function of stunned myocardium. Despite an improvement in ventricular function, levosimendan does not increase myocardial oxygen uptake significantly. An increase in coronary blood flow and a reduction in coronary vascular resistance have been observed. Levosimendan reduces plasma brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels substantially, and a decrease in plasma endothelin-1 has been observed. Levosimendan also exerts beneficial effects on proinflammatory cytokines and apoptosis mediators. The effects of a 24-hour levosimendan infusion on filling pressure, ventricular function and BNP, as well as NT-proBNP, last for at least 7 days.

1. **Administration:**

Infusion is often started at a dose of 0.1 mg/kg/min and titrated to 0.2 mg/kg/min as long as systolic blood pressure remains stable after the first 2–3 hours. The recommended interval of infusion in acute heart failure is 24 hours. Initial bolus of levosimendan is not usually given, in order to prevent risk of hypotension in patients who have systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg (4).

1. **Hemodynamics and Neurohormonal Effects:**

Levosimendan produces significant, dose-dependent increases in cardiac output (CO) and stroke volume, and decreases in pulmonary capillary wedge pressure (PCWP), mean blood pressure (BP), mean pulmonary artery pressure (PAP), mean right atrial pressure, and total peripheral resistance. These effects are registered rapidly (within a few minutes of starting infusion). There is no evidence of the development of tolerance or attenuation of effect even after infusions up to 48 h in duration. The presence of the long-acting metabolite designated OR-1896 means that these core haemodynamic effects persist for several days after termination of levosimendan infusion and for much longer than with dobutamine (5).

The increase in CO evoked by levosimendan is similar to that achieved with dobutamine at comparable doses but the reduction in PCWP produced by levosimendan is considerably greater. Moreover, and in contrast to dobutamine, the haemodynamic effects of levosimendan are not attenuated by concomitant beta-blocker use. This difference contributes to the position of the 2016 ESC HF guidelines that levosimendan should be the preferred agent when inotropy is indicated for an HF patient pretreated with a beta-blocker (6).

Levosimendan should be used with caution—and with no bolus dose—in patients with low baseline SBP (<100 mmHg) or diastolic blood pressure (DBP, <60 mmHg), or those at risk of a hypotensive episode. Patients who might be considered ineligible for levosimendan therapy on these grounds account for <10% of the AHF population according to the 2016 ESC guidelines. Hypovolaemia should be corrected prior to levosimendan infusion, as a precautionary measure (7).

Rapid and sustained reduction in levels of natriuretic peptides is a hallmark of levosimendan use in clinical trials. Levosimendan infusion in the REVIVE II study was associated with a marked and sustained reduction in circulating brain natriuretic peptide levels. Correlations between discharge brain natriuretic peptide (BNP) and longer-term clinical prognosis are not always resilient or persistent, and it would be imprudent to assume from its effect on BNP alone that levosimendan is certain to have an enduring impact on prognosis in all cases (8).

1. **Adverse Effects:**

Levosimendan has been well tolerated in patients with acute left heart failure or those who underwent cardiac surgery. Common adverse effects reported are hypotension, headache, and dizziness secondary to the vasodilating properties. Increased incidence of atrial fibrillation has also been associated with infusion of levosimendan compared with both dobutamine and placebo (9).

1. **Uses in Cardiac Surgery:**

In the past years, numerous studies have suggested that levosimendan could exert a favorable action when it is administered perioperatively in heart surgery patients. The majority of RCTs compared perioperative levosimendan administration to placebo or other inotropes (mainly dobutamine and milrinone) in heart surgery context. Other studies investigated the optimal time of administration of levosimendan. Some studies involved pediatric patients referred to heart surgery (10).

1. **Studies *Versus* conventional drugs**

In 2006 **Tritapepe *et al*.** in a pilot trial, examined the effect of the short administration of levosimendan (24 mcg/Kg over 10 min before cardiopulmonary by-pass placement) *versus* conventional drugs in patients who underwent CABG in elective surgery for stable angina. Interestingly, postoperative Troponine I levels were significantly lower in patients in the levosimendan arm which showed also a higher cardiac index after heart surgery. Three years later, the authors confirmed such observations in a larger randomized double-blind study recruiting one hundred and six patients referred to elective CABG surgery. Of note, in this larger trial, intubation time, Intensive Care Unit (ICU) stay and need for inotropic support were significantly reduced in patients who received levosimendan infusion (11).

In 2014, levosimendan was used as a pretreatment (24 hours infusion) in a randomized study involving 50 patients undergoing off-pump coronary artery bypass grafting (OPCAB) with Left Ventricular Ejection Fraction (LVEF) < 30%. Levosimendan arm was characterized by less need of Cardiopulmonary Bypass (CPB) and Intra-aortic Balloon Pump (IABP) than placebo. Moreover, levosimendan pretreatment was associated with a shorter stay in ICU (13).

1. **Best Time of Administration**

**(Eris *et al*.)** investigated the optimal time of levosimendan administration in a retrospective study of forty patients with left ventricular dysfunction (LVEF less than 35%) referred to CABG. we found that infusion of the drug before surgery (0.2 mcg/kg/min 12 hours before the operation) was associated with lower mortality and better improvement of heart function compared to control group and to groups of patients who received levosimendan after induction of anesthesia and during weaning of cardiopulmonary bypass. Similarly, another retrospective analysis conducted in 159 cardiac surgery patients found that early administration of levosimendan reduced mortality and morbidity compared to late start of treatment (one hour after admission in ICU) (14).

In another study of forty-five patients who underwent heart surgery, administration of levosimendan during or after intervention ameliorated stroke volume and cardiac index. In the same study, ICU and hospital stay were significantly shorter in patients who started drug infusion in the operating theater (15).

1. Studies *Versus* Other Inotropes

Several studies involving heart surgery patients, have investigated the efficacy and safety of the perioperative administration of levosimendan compared to other inotropes. In 2006, Alvarez *et al*. performed a study of 41 patients with low cardiac output after cardiopulmonary by-pass. Patients were randomly assigned to 24 hours infusion of dobutamine or levosimendan. Authors found that both drugs were able to increase cardiac index, but the increase induced by levosimendan was significantly greater (2.9 l/min per m2 *vs.* 2.4 l/min per m2 in dobutamine group at 24 h; p<0.05) (16).

Several meta-analyses of studies investigating the effect of levosimendan administration in context of cardiac surgery confirmed significant benefits from perioperative drug infusion, ranging from reduction of ICU stay to improved survival. Interestingly, patients with impaired systolic function benefited the most from levosimendan. Moreover, better nephrological outcomes (*i.e*. less need for dialysis and a lower rate of development of acute kidney injury) were observed in subjects who received perioperative levosimendan (17).

Patients and Methods

This study was reviewed and approved by IRB, ethics committee or audit department of Critical care department of the faculty of medicine, Cairo University. The study runs in concordance with international ethical standards and applicable local regulatory guidelines. The study does not have any physical, psychological, social, legal, economic, or any other anticipated risks to study’s participants. The study conserves participants’ privacy. Investigators are responsible for keeping the security of the data. Also, the participants’ data were not used for any other purpose outside this study. Personal data (e.g. Name, Contact info) were not entered in our data entry software to conserve the participants' privacy, however, each subject got a unique identifier code.

A written informed consent was obtained from every eligible patient before being included in the study. Patients were informed about the study objectives, methodology, risk, and benefit.

**Study Design and Setting:**

The present study was a prospective cohort study that carried out from March to September 2018 at Agouza Police hospital. The eligible patients were divided into two groups:

* Group A which included patients who received intravenous levosimendan (at a dose of 0.2 μg per kilogram of body weight per minute for 1 hour, followed by a dose of 0.1 μg per kilogram per minute for 23 hours), with the infusion started before surgery.
* Group B which included patients who received conventional drugs.

**Inclusion and Exclusion Criteria:**

We included patients who fulfilled the following criteria:

* Patients undergoing isolated CABG or CABG with valve (Aortic and / or Mitral) replacement.
* Age group between 18 and 70 years old.
* Patients with LV dysfunction with EF ≤ 35%.

We excluded

* Patients with normal LV functions undergoing CABG
* Patients diagnosed preoperatively with AF or have history of AF.
* Patients with end stage renal disease (ESRD) on hemodialysis.
* Patients who refuse to participate in the study.

**Sample Size and Sampling:**

Using PASS program, setting alpha error at 5% and power 80%. Results from previous study (**Ducceschi et al., 1999**) showed that four-component primary end point occurred in patients assigned to receive levosimendan and in patients assigned to receive conventional drugs. Based on this, the needed sample was 100 case undergoing CABG (50 per each group). We utilized a consecutive sampling technique within the time of the study to collect the predetermined sample size.

**Study’s Procedure and Data Collection:**

The following data were collected from every eligible participants.

* Full history taking and clinical examination.
* Echocardiography pre-operative & post-operative after 48hours.
* Laboratory pre-operative & post-operative.
* Dobutamine stress echocardiography pre-operative.
* Data collection to evaluate incidence of complications postoperative in ICU.
* Daily evaluate of renal functions.
* Incidence of perioperative cardiac events.

After the insertion of an arterial catheter and before skin incision, an intravenous infusion of levosimendan was started at a dose of 0.2 μg per kilogram of body weight per minute for 1 hour, and the dose was then reduced to 0.1 μg per kilogram per minute for another 23 hours. The use of concomitant medications, including other inotropes and vasopressors, was left to the discretion of treating physicians.

**Study’s Outcomes**:

The two primary end points were a four-component composite of death through day 30, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of an Intraaortic balloon pump through day 5; and a two-component composite of death through day 30 or use of an Intraaortic balloon pump through day 5. Secondary outcomes were length of intensive care unit (ICU) stay, postoperative arrythmia, and postoperative renal replacement therapy.

**Statistical Analysis**:

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). The normality of the data were assessed using Shapiro-Wilk Test. Numerical data were described as mean ±SD if normally distributed; or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Independent Student t-test and paired t-test were used to compare parametric quantitative variables; while Mann-Whitney tests and Wilcoxon matched pairs test were used to compare non-parametric quantitative variables. Chi-square test or McNemar-Bowker tests were used to analyze categorical variables. Multilinear logistic regression was undertaken to assess the predictors of study’s outcomes. A p-value < 0.05 is considered statistically significant.

Results

In the present study, we included 100 patients with LV dysfunction during their post-CABG ICU stay. The patients were randomized into the following groups:

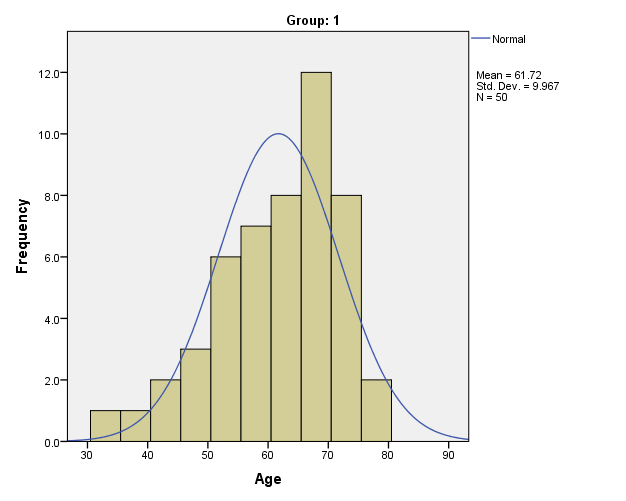
* Group A which included 50 patients who received intravenous levosimendan (at a dose of 0.2 μg per kilogram of body weight per minute for 1 hour, followed by a dose of 0.1 μg per kilogram per minute for 23 hours), with the infusion started before surgery.
* Group B which included patients who received conventional drugs.

**Table 3: The demographic characteristics of the included patients in levosimendan group**

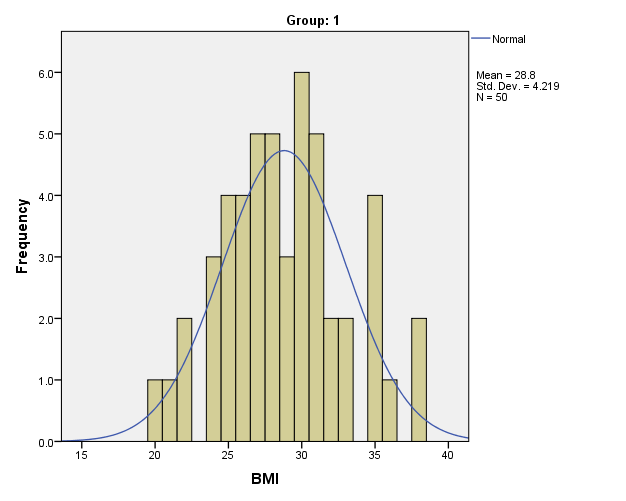
|  |  |
| --- | --- |
| **Variables** | **Patients (N =50)** |
| **Age in years**   * Mean ±SD * Median (Range) | 61.72 ±9.9  65 (33 -78) |
| **BMI in Kg/m2**   * Mean ±SD * Median (Range) | 28.8 ±4.2  28.5 (20 - 38) |
| **Gender, No (%)** |  |
| * Male | 39 (78%) |
| * Female | 11 (22%) |
| **Comorbidities, No (%)** |  |
| * DM | 11 (22%) |
| * HTN | 33 (66%) |
| * HTN and DM | 6 (12%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (3) shows that the mean age of the patients within levosimendan was 61.72 ±9.9 years and the majority of patients were males (78%). The mean BMI was 28.8 ±4.2kg/m2. Almost 12% of the patients had diabetes plus hypertension, and 66% had hypertension.



**Figure 5: Distribution of Age**



**Figure 6: Distribution of BMI**

**Table 4: The preoperative medications of the included patients in evosimendan group**

|  |  |
| --- | --- |
| **Variables** | **Patients (N =50))** |
| **Preoperative BB, No (%)** |  |
| * Yes | 30 (60%) |
| * No | 20 (40%) |
| **Preoperative ACE, No (%)** |  |
| * Yes | 20 (40%) |
| * No | 30 (60%) |
| **Preoperative CCB, No (%)** |  |
| * Yes | 4 (8%) |
| * No | 46 (92%) |
| **Preoperative statin, No (%)** |  |
| * Yes | 33 (66%) |
| * No | 17 (33%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (4) shows that 60% of the patients were on preoperative BB, 40% on ACE inhibitors, 8% on CCB, and 66% on preoperative statin.

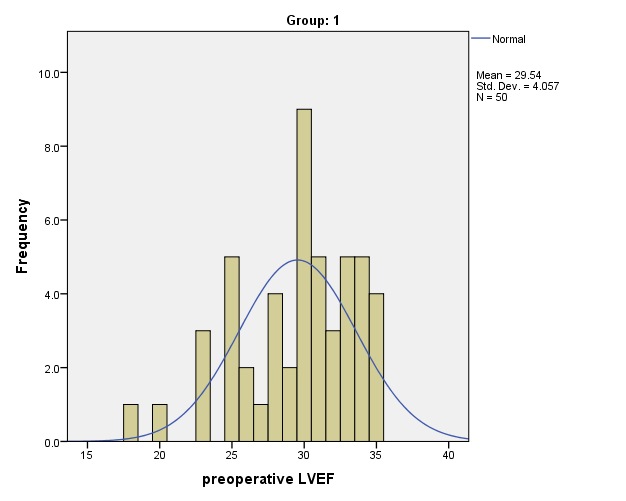
**Figure 7: Distribution of preoperative medications**

**Table 5: The preoperative cardiac function of the included patients in levosimendan group**

|  |  |
| --- | --- |
| **Variables** | **Patients (N =50)** |
| **LVEF in %**   * Mean ±SD * Median (Range) | 29.54 ±9.9  30 (18 -35) |
| **Aortic valve gradient**   * Mean ±SD * Median (Range) | 45 ±5  45 (40 - 50) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (5) shows that the preoperative LVEF of the patients within levosimendan was 29.54 ±9.9%. The mean aortic valve gradient was 45 ±5.



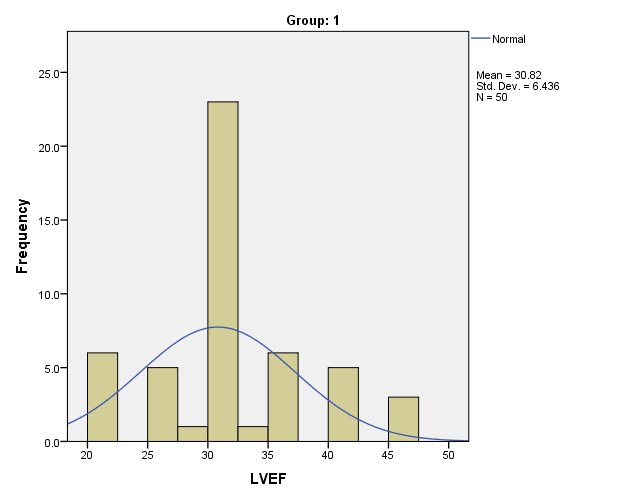
**Figure 8: Distribution of preoperative LVEF**

**Table 6: The postoperative cardiac function of the included patients in levosimendan group**

|  |  |
| --- | --- |
| **Variables** | **Patients (N =50)** |
| **LVEF in %**   * Mean ±SD * Median (Range) | 30.82 ±6.4  30 (20 -45) |
| **Heart rate in beats/min**   * Mean ±SD * Median (Range) | 77.1 ±7.1  75 (65 - 90) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (6) shows that the postoperative LVEF of the patients within levosimendan was 30.82 ±6.4%. The mean heart rate was 77.1 ±7.1 beats/min.



**Figure 9: Distribution of postoperative LVEF**

**Table 7: Primary outcomes of the included patients in levosimendan group**

|  |  |
| --- | --- |
| **Variables** | **Patients (N =50)** |
| **Death at 30 days, No (%)** |  |
| * Yes | 9 (18%) |
| * No | 41 (82%) |
| **Renal-replacement therapy at 30 days, No (%)** |  |
| * Yes | 4 (8%) |
| * No | 46 (92%) |
| **Myocardial infarction, No (%)** |  |
| * Yes | 8 (16%) |
| * No | 42 (84%) |
| **Use of mechanical cardiac assist device, No (%)** |  |
| * Yes | 15 (30%) |
| * No | 35 (70%) |
| **Four-component end point, No (%)** |  |
| * Yes | 17 (34%) |
| * No | 33 (66%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (5) shows that the mortality rate at 30 days was 18% and the incidence of RRT was 8%. Eight (16%) patients had myocardial infarction and 30% of the patients used mechanical cardiac assist device. The overall incidence of four-component end point was 34%.

**Figure 10: Distribution of primary outcomes**

**Table 8: Secondary outcomes of the included patients in levosimendan group**

|  |  |
| --- | --- |
| **Variables** | **Patients (N =50)** |
| **Postoperative inotropes, No (%)** |  |
| * Yes | 50 (100%) |
| * No | 0 |
| **Postoperative Arrythmia, No (%)** |  |
| * Yes | 24 (48%) |
| * No | 26 (52%) |
| **Complications, No (%)** |  |
| * Yes | 31 (62%) |
| * No | 19 (38%) |
| **Type of complications, No (%)** |  |
| * Renal impairment | 6 (12%) |
| * Renal impairment | 1 (2%) |
| * Stroke | 1 (2%) |
| * VF | 1 (2%) |
| * Elevated kidney and/or liver function | 13 (26%) |
| * Elevated cardiac enzymes | 6 (12%) |
| * Psychosis | 3 (6%) |
| **ICU Stay in days** |  |
| * Mean ±SD * Median (Range) | 3.92 ±1.8  4 (1 -10) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (8) shows that the incidence of postoperative arrythmia was 24%. Thirty-one (62%) patients had postoperative complications. The mean ICU stay was 3.92 ±1.8 days.

**Figure 11: Distribution of secondary outcomes**

**Table 9: The difference in demographic characteristics between studied groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Group A (N =50)** | **Group B (N =50)** | **P-value** |
| **Age in years**   * Mean ±SD * Median (Range) | 61.72 ±9.9  65 (33 -78) | 59.8 ±8.1  64 (44 -69) | 0.29 |
| **BMI in Kg/m2**   * Mean ±SD * Median (Range) | 28.8 ±4.2  28.5 (20 - 38) | 27.02 ±3.7  28 (22 - 31) | 0.36 |
| **Gender, No (%)** |  |  |  |
| * Male | 39 (78%) | 43 (86%) | 0.21 |
| * Female | 11 (22%) | 7 (14%) |
| **Comorbidities, No (%)** |  |  |  |
| * DM | 11 (22%) | 10 (20%) | 0.71 |
| * HTN | 33 (66%) | 34 (68%) |
| * HTN and DM | 6 (12%) | 6 (12%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (9) shows that there were no statistically significant differences between studied groups in terms of age (p =0.29), BMI (p =0.36), gender (p =0.21), and comorbidities (p =0.71).

**Table 10: The** **difference in preoperative medications among studied groups.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Group A (N =50)** | **Group B (N =50)** | **P-value** |
| **Preoperative BB, No (%)** |  |  |  |
| * Yes | 30 (60%) | 29 (58%) | 0.83 |
| * No | 20 (40%) | 21 (42%) |
| **Preoperative ACE, No (%)** |  |  |  |
| * Yes | 20 (40%) | 29 (58%) | 0.072 |
| * No | 30 (60%) | 21 (42%) |
| **Preoperative CCB, No (%)** |  |  |  |
| * Yes | 4 (8%) | 0 | 0.04 |
| * No | 46 (92%) | 50 (100%) |
| **Preoperative statin, No (%)** |  |  |  |
| * Yes | 33 (66%) | 35 (70%) | 0.72 |
| * No | 17 (33%) | 15 (30%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (10) shows that there were no statistically significant differences between studied groups in terms of preoperative BB (p =0.83), preoperative ACE inhibitors (p =0.07), and preoperative statin (p =0.72). On the other hand, there was statistically significant difference between studied groups in terms of preoperative CBB (p =0.04).

**Table 11: The difference in preoperative cardiac function among studied groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Group A (N =50)** | **Group B (N =50)** | **P-value** |
| **LVEF in %**   * Mean ±SD * Median (Range) | 29.54 ±9.9  30 (18 -35) | 30.1 ±3.2  30 (26 -35) | 0.445 |
| **Aortic valve gradient**   * Mean ±SD * Median (Range) | 45 ±5  45 (40 - 50) | 45 ±5  45 (40 - 50) | ---- |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (11) shows that there were no statistically significant differences between studied groups in terms of preoperative LVEF (p =0.445) and preoperative aortic valve gradient.

**Table 12: The difference in postoperative cardiac function of the studied groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Group A (N =50)** | **Group B (N =50)** | **P-value** |
| **LVEF in %**   * Mean ±SD * Median (Range) | 30.82 ±6.4  30 (20 -45) | 33.32 ±7.4  33 (20 -45) | 0.075 |
| **Heart rate in beats/min**   * Mean ±SD * Median (Range) | 77.1 ±7.1  75 (65 - 90) | 86.46 ±14.5  86.5 (55 - 120) | 0.001 |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (12) shows that there was no statistically significant difference between studied groups in terms of postoperative LVEF (p =0.445). On the contrary, there was statistically significant difference between studied groups in terms of postoperative heart rate (p =0.001). Patients in levosimendan group had significantly lower heart rate.

**Table 13: The difference in primary outcomes among studied groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Group A (N =50)** | **Group B (N =50)** | **RR, 95% CI** | **P-value** |
| **Death at 30 days, No (%)** |  |  |  |  |
| * Yes | 9 (18%) | 22 (44%) | 0.41 (0.21 - 0.79) | 0.004 |
| * No | 41 (82%) | 28 (56%) |
| **Renal-replacement therapy at 30 days, No (%)** |  |  |  |  |
| * Yes | 4 (8%) | 4 (8%) | ---- | ---- |
| * No | 46 (92%) | 46 (92%) |
| **Myocardial infarction, No (%)** |  |  |  |  |
| * Yes | 8 (16%) | 7 (14%) | 1.14 (0.45 - 2.91) | 0.72 |
| * No | 42 (84%) | 43 (86%) |
| **Use of mechanical cardiac assist device, No (%)** |  |  |  |  |
| * Yes | 15 (30%) | 22 (44%) | 0.68 (0.41 - 1.15) | 0.107 |
| * No | 35 (70%) | 28 (56%) |
| **Four-component end point, No (%)** |  |  |  |  |
| * Yes | 17 (34%) | 22 (44%) | 0.77 (0.47 - 1.27) | 0.21 |
| * No | 33 (66%) | 28 (56%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (13) shows that there were no statistically significant differences between studied groups in terms of RRT, myocardial infarction (p =0.72), and use of mechanical cardiac assist device (p =0.107). On the contrary, there was statistically significant difference between studied groups in terms of 30 days mortality (p =0.004). Patients in levosimendan group had significantly lower mortality rate.

**Table 14: The difference in secondary outcomes among studied groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Group A (N =50)** | **Group B (N =50)** | **RR, 95% CI** | **P-value** |
| **Postoperative inotropes, No (%)** |  |  |  |  |
| * Yes | 50 (100%) | 50 (100%) | ---- | ---- |
| * No | 0 | 0 |
| **Postoperative Arrythmia, No (%)** |  |  |  |  |
| * Yes | 24 (48%) | 22 (44%) | 1.1 (0.71 - 1.66) | 0.68 |
| * No | 26 (52%) | 28 (56%) |
| **Complications, No (%)** |  |  |  |  |
| * Yes | 31 (62%) | 36 (72%) | 0.86 (0.65 -1.13) | 0.25 |
| * No | 19 (38%) | 14 (28%) |
| **ICU Stay in days** |  |  |  |  |
| * Mean ±SD * Median (Range) | 3.92 ±1.8  4 (1 -10) | 4.92 ±1.5  4 (3 -7) | ----- | 0.002 |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (14) shows that there were no statistically significant differences between studied groups in terms of postoperative inotropes, postoperative arrythmia (p =0.68), and incidence of complications (p =0.25). On the contrary, there was statistically significant difference between studied groups in terms of ICU stay (p =0.002). Patients in levosimendan group had significantly shorter ICU stay.

**Table 15: The difference in demographic characteristics according to mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Dead (N =9)** | **Alive (N =41)** | **P-value** |
| **Age in years**   * Mean ±SD * Median (Range) | 62.67 ±9.9  65 (50 -78) | 61.5 ±10.2  65 (33 -76) | 0.98 |
| **BMI in Kg/m2**   * Mean ±SD * Median (Range) | 28.4 ±3.7  28 (21 - 33) | 28.9 ±3.3  289 (20 - 38) | 0.99 |
| **Gender, No (%)** |  |  |  |
| * Male | 7 (77.8%) | 32 (78%) | 0.98 |
| * Female | 2 (22.2%) | 9 (22%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (15) shows that there were no statistically significant differences between studied groups in terms of age (p =0.29), BMI (p =0.36), gender (p =0.21), and comorbidities (p =0.71).

**Table 16: The difference in preoperative medications according to mortality.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Dead (N =9)** | **Alive (N =41)** | **P-value** |
| **Preoperative BB, No (%)** |  |  |  |
| * Yes | 30 (60%) | 29 (58%) | 0.83 |
| * No | 20 (40%) | 21 (42%) |
| **Preoperative ACE, No (%)** |  |  |  |
| * Yes | 20 (40%) | 29 (58%) | 0.072 |
| * No | 30 (60%) | 21 (42%) |
| **Preoperative CCB, No (%)** |  |  |  |
| * Yes | 4 (8%) | 0 | 0.04 |
| * No | 46 (92%) | 50 (100%) |
| **Preoperative statin, No (%)** |  |  |  |
| * Yes | 33 (66%) | 35 (70%) | 0.72 |
| * No | 17 (33%) | 15 (30%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (10) shows that there were no statistically significant differences between studied groups in terms of preoperative BB (p =0.83), preoperative ACE inhibitors (p =0.07), and preoperative statin (p =0.72). On the other hand, there was statistically significant difference between studied groups in terms of preoperative CBB (p =0.04).

**Table 17: The difference in preoperative cardiac function according to mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Dead (N =9)** | **Alive (N =41)** | **P-value** |
| **LVEF in %**   * Mean ±SD * Median (Range) | 29.54 ±9.9  30 (18 -35) | 30.1 ±3.2  30 (26 -35) | 0.445 |
| **Aortic valve gradient**   * Mean ±SD * Median (Range) | 45 ±5  45 (40 - 50) | 45 ±5  45 (40 - 50) | ---- |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (11) shows that there were no statistically significant differences between studied groups in terms of preoperative LVEF (p =0.445) and preoperative aortic valve gradient.

**Table 18: The difference in postoperative cardiac function according to mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Dead (N =9)** | **Alive (N =41)** | **P-value** |
| **LVEF in %**   * Mean ±SD * Median (Range) | 30.82 ±6.4  30 (20 -45) | 33.32 ±7.4  33 (20 -45) | 0.075 |
| **Heart rate in beats/min**   * Mean ±SD * Median (Range) | 77.1 ±7.1  75 (65 - 90) | 86.46 ±14.5  86.5 (55 - 120) | 0.001 |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (12) shows that there was no statistically significant difference between studied groups in terms of postoperative LVEF (p =0.445). On the contrary, there was statistically significant difference between studied groups in terms of postoperative heart rate (p =0.001). Patients in levosimendan group had significantly lower heart rate.

**Table 19: The difference in primary outcomes according to mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Dead (N =9)** | **Alive (N =41)** | **P-value** |
| **Renal-replacement therapy at 30 days, No (%)** |  |  |  |
| * Yes | 4 (8%) | 4 (8%) | ---- |
| * No | 46 (92%) | 46 (92%) |
| **Myocardial infarction, No (%)** |  |  |  |
| * Yes | 8 (16%) | 7 (14%) | 0.72 |
| * No | 42 (84%) | 43 (86%) |
| **Use of mechanical cardiac assist device, No (%)** |  |  |  |
| * Yes | 15 (30%) | 22 (44%) | 0.107 |
| * No | 35 (70%) | 28 (56%) |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (13) shows that there were no statistically significant differences between studied groups in terms of RRT, myocardial infarction (p =0.72), and use of mechanical cardiac assist device (p =0.107). On the contrary, there was statistically significant difference between studied groups in terms of 30 days mortality (p =0.004). Patients in levosimendan group had significantly lower mortality rate.

**Table 20: The difference in secondary outcomes according to mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Dead (N =9)** | **Alive (N =41)** | **P-value** |
| **Postoperative inotropes, No (%)** |  |  |  |
| * Yes | 50 (100%) | 50 (100%) | ---- |
| * No | 0 | 0 |
| **Postoperative Arrythmia, No (%)** |  |  |  |
| * Yes | 24 (48%) | 22 (44%) | 0.68 |
| * No | 26 (52%) | 28 (56%) |
| **Complications, No (%)** |  |  |  |
| * Yes | 31 (62%) | 36 (72%) | 0.25 |
| * No | 19 (38%) | 14 (28%) |
| **ICU Stay in days** |  |  |  |
| * Mean ±SD * Median (Range) | 3.92 ±1.8  4 (1 -10) | 4.92 ±1.5  4 (3 -7) | 0.002 |

\*Data are presented as mean ±SD, median (Range), or number (%).

Table (14) shows that there were no statistically significant differences between studied groups in terms of postoperative inotropes, postoperative arrythmia (p =0.68), and incidence of complications (p =0.25). On the contrary, there was statistically significant difference between studied groups in terms of ICU stay (p =0.002). Patients in levosimendan group had significantly shorter ICU stay.

**Table 21: Multivariate analysis of factors associated with mortality.**

|  | **Odds ratio** | **95% confidence interval** | **P- Value** |
| --- | --- | --- | --- |
| Age in years | 0.948 | 0.908- 1.98 | 0.114 |
| LOS | 0.785 | 0.611 – 1.008 | 0.058 |
| RBG at admission | 0.997 | 0.989 – 1.005 | 0.455 |
| Lactate at admission | 1.045 | 0.779 – 1.42 | 0.771 |

\*Data are presented as odds ratio and 95% confidence interval

.

Discussion

Postoperative atrial fibrillation (POAF) is common both after cardiothoracic and noncardiothoracic surgery. In patients undergoing cardiothoracic surgery, its incidence is 16–46%, which varies according to the extent of postoperative monitoring used and the specific surgical procedures. While in noncardiothoracic surgery, the incidence varies between 0.4% and 12%. POAF occurs during the postoperative course, with a peak between second and fifth postoperative day(**Greenberg et al.**, **2017**).

POAF is self-limiting, but it may be lead to hemodynamic derangements, postoperative stroke, perioperative myocardial infarction, ventricular arrhythmias, and heart failure. Moreover, POAF can lead to a longer hospital stay, greater morbidity and mortality, and increased costs(**Attaran et al.**, **2011**).

General risk factors for POAF are old age, male gender, obesity, preexisting congestive heart failure, chronic renal failure, or COPD. In noncardiothoracic surgery, predictors for POAF are preexisting valvular disease, asthma, intra-abdominal and major vascular surgery, and intraoperative hypotension.

Atrial fibrillation within the first 5 days after CABG is relatively common with rates of 20% to 50% and is associated with increased morbidity with a higher risk of embolic stroke postoperatively as well as increased mortality(**Dobrev et al.**, **2019**).

Therefore, we conducted our prospective cohort study to determine the effect of certain predictors on incidence of POAF during the stay after CABG. We included 123 patients with coronary artery disease (CAD) undergoing CABG. Most of them were smoker male with mean age 57.4 ±8.7 years and left atrial (LA) diameter was 4.1 ±0.52 cm.

**McNeely and colleagues** (**2017**) examined the trends in patient characteristics and outcomes in patients who underwent CABG over a 12-year period in the Medicare database. The study included 1,264,265 isolated CABG procedures during the period from January 2000 through November 2012. The majority of patients were old men with age of 74 (70–78) years.

Regarding the laboratory parameters, the mean serum K+ level changed significantly over the postoperative endpoints (p <0.001). In addition, serum Mg level changed significantly over the postoperative endpoints (p <0.001).

In agreement with our findings, **Pasternak and colleagues** (**2006**) analyzed the changes in blood Mg levels in 20 male patients undergoing CABG with extracorporeal circulation. The results showed that blood Mg++ decreased during extracorporeal circulation and immediately after surgery and increased in the morning of the first and second postoperative days. The authors concluded that the CABG with extracorporeal circulation resulted in a significant decrease in blood Mg concentration.

Similarly, **Booth and colleagues** (**2003**) investigated the relationship between serum magnesium levels and major adverse cardiac events (MACE) after CABG. The results showed that the serum magnesium level decreased significantly after CABG. Notably, a serum magnesium level <1.8 mmol/L decreased the event-free survival rate (2-fold increased risk of death or myocardial infarction at 1 year.

Regarding the incidence of POAF, it was reported in 40 (32.5%) patients in our study.

In a retrospective study by **Ferreira and colleagues** (**2017**) included all CABG surgeries performed in a tertiary centre, between 2004 and 2011. A total of 2511 patients, with mean age of 63±10 years and 78.7% males were included. The authors reported that POAF occurred in 450 patients (18.0%).

Also, **Najafi and colleagues** (**2007**) in a prospective study on 170 patients found that 53 patients developed POAF (31%).

Again, **Maslow and colleagues** (**2000**) in a retrospective study on 124 patients found that 24 patients (22%) had POAF.

Regarding predictors of POAF, our results showed that there were statistically significant difference between POAF and non-POAF groups in terms of age (p =0.039), sex (p <0.001), and LA diameter (p <0.001). Patients with POAF were significantly older and had higher LA diameter. Also, the logistic regression showed that female sex was an independent predictor of POAF.

In a prospective study, **Gorczyca and colleagues** (**2018**) found that the average age of POAF patients was significantly higher than non-POAF controls; The univariate analysis revealed age over 69 years was a predictor of POAF.

Moreover, **Luo and colleagues** (**2017**) performed a prospective study to determine the risk factors of POAF in patients who underwent isolated on-pump CABG.The incidence of POAF was 23.36%; patients with POAF were significantly older and have larger left atrium diameter. The Logistic regression analyses showed that a left atrium diameter was a significant predictor of POAF.

Our study showed that there were statistically significant difference between POAF and non-POAF groups in terms of valve replacement (p =0.001), CHA2DS2-VASc score (p <0.001), and postoperative inotropics (p =0.011). Patients with POAF were more likely to have valve replacement and postoperative inotropics. Also, patients with POAF had significantly higher CHA2DS2-VASc score.

In agreement with our findings, **Haghjoo and colleagues** (**2008**) conducted a prospective study to identify the preoperative, intraoperative, and postoperative predictors of AF in a pure cohort of the patients with coronary artery disease who underwent CABG surgery. POAF occurred in 46 (15%) of patients. By univariate analysis, older age, larger LA, and adrenergic use in ICU were significantly associated with occurrence of post-CABG AF (all P< 0.05). However, in the logistic regression model, age, LA dimension, and postoperative adrenergic use remained independently predictive of POAF.

**Ismail and colleagues** (**2017**) performed a retrospective cohort study on 252 consecutive adult patients underwent CABG, in King Faisal Specialist Hospital and Research Center in Jeddah, Saudi Arabia. Eight-three patients (49.4%) were diabetics in group A and 56 patients (66.7%) in group B (P = .0001). Patients who developed POAF had a lower ejection fraction (44.8 ± 5.7%), diastolic dysfunction, and larger Left atrial volume.

On the other hand, there were no statistically significant difference between POAF and non-POAF groups in terms of K+ and Mg++ at any time points (p >0.05). But, patients without POAF had significant changes in serum K+ and level at study time points (p =0.001).

Similar to our findings, **Najafi and colleagues** (**2007**) reported that there was a significant difference between in serum Mg level on three occasions between patients with and without POAF.

**Study Limitations**:

We acknowledge that the present study has limitations. The sample size of our cohort was relatively small which may impair the generalizability of our findings. Moreover, long-term patient centered outcomes were not included in our study.

Conclusion

The incidence of POAF following CABG surgery is almost 32%. There are a wide range of significant epidemiological, clinical, and operative predictors for the development of post-CABG AF including older age, female gender, large LA diameter, valve replacement, higher CHA2DS2-VASc score, and postoperative inotropics. However, only female gender and valve replacement were independent predictors of POAF. Nevertheless, further large-scale studies are still needed to confirm our findings.

Summary

Postoperative atrial fibrillation (POAF) is common both after cardiothoracic and noncardiothoracic surgery. In patients undergoing cardiothoracic surgery, an incidence of 16–46% has been reported depending on the extent of postoperative monitoring used and the specific surgical procedures. Even though POAF can be self-limiting, it may be associated with hemodynamic derangements, postoperative stroke, perioperative myocardial infarction, ventricular arrhythmias, and heart failure. Risk of developing POAF may be related to several factors.

Therefore, we conducted our prospective cohort study to determine the effect of certain predictors on the incidence of POAF during the ICU stay after CABG. We included 123 patients with coronary artery disease (CAD) undergoing CABG. Most of them were smoker male with mean age 57.4 ±8.7 years. Regarding the incidence of POAF, we found that the POAF was reported in 40 (32.5%) patients in the present study. There were statistically significant associations between POAF and older age (p =0.031) and higher LA diameter (p <0.001). Patients with POAF were significantly older and had higher LA diameter. In contrary, there were no statistically significant difference between POAF and non-POAF groups in terms of K+ at any time points (p >0.05). Similarly, there were no statistically significant difference between POAF and non-POAF groups in terms of Mg level at any time points (p >0.05). There was statistically significant association between POAF and sex (p <0.001); patients with POAF were more likely to be females. There was no statistically significant association between POAF and smoking (p =0.123). There was statistically significant association between POAF and CHA2DS2,VAS (p <0.001); patients with POAF were more likely to have higher score.

The logistic regression showed that left atrial diameter (p <0.001), Mg++ level at 72 hours (p =0.04), CHA2DS2.VAS (p =0.006), and female sex were independent predictors of POAF.

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