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Levosimendan Use Decreases Atrial Fibrillation in Patients after Coronary Artery Bypass Grafting: A Pilot Study

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ABSTRACT

Background: Atrial fibrillation (AF) often occurs after coronary artery bypass grafting (CABG) and can result in increased morbidity and mortality due to complications. In the present study, our goal was to investigate whether the use of levosimendan can reduce the frequency of AF after coronary artery bypass grafting in patients with poor left ventricle function.

Material and Methods: To investigate the effectiveness of levosimendan in the prophylaxis of AF, we conducted a prospective, randomized, placebo-controlled clinical study on 200 consecutive patients in whom we performed elective CABG operations. Baseline characteristics were similar in both groups. A control group of 100 patients were treated with placebo (500 mL saline solution), whereas the levosimendan group (n = 100 patients) was treated with levosimendan. High-sensitivity C-reactive protein, cardiac troponin, and creatine kinase–MB levels were measured before surgery and 5 days postoperatively.

Results: AF occurred in 12% of the levosimendan group and 36% of the control group. The occurrence of AF was significantly lower in the levosimendan group ($P < 0.05$). The duration of AF in the levosimendan group was significantly shorter than that in the control group (4.83 ± 1.12 and 6.50 ± 1.55 hours, respectively; $P = 0.028$). Our research showed that C-reactive protein was higher postoperatively in the control group than in the levosimendan group ($P < 0.05$).

Conclusions: The incidence of postoperative AF in the levosimendan group was reduced significantly in patients with poor left ventricle function after CABG operations.

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INTRODUCTION

Atrial and ventricular arrhytmias have been recognized as the most common arrhythmias after coronary artery bypass grafting (CABG). The reported incidence of atrial fibrillation (AF) after CABG surgery varies from 20% to 40%, with the arrhythmia usually occurring between the second and fourth postoperative days [Leitch 1990; Creswell 1993; Aranki 1996; Almassi 1997; Svedjeholm 2000; Mahoney 2002]. Although this arrhythmia is usually benign and self-limiting, it may result in hemodynamic instability, thromboembolic events, longer hospital stay, and increased healthcare costs [Creswell 1993; Almassi 1997; Hakala 2002]. Therefore much attention has focused on the prevention of AF in high-risk patients. For the correction of AF a number of medical and surgical approaches have previously been researched. However, there are no data in the literatureabout the efficacy of levosimendan for the prevention of AF after CABG.

Levosimendan, a pyridazinone-dinitrite and a member of a new class of agents, the calcium sensitizers, that increase myocardial contractility without increasing intracellular calcium, has emerged as an inotropic agent. Levosimendan use in cardiac surgery provides myocardial preconditioning and vasodilating effects without intracellular calcium accumulation during ischemia-reperfusion injury. Levosimendan provides peripheral vasodilation, coronary artery dilation, and myocyte mitochondrial activation resulting from adenosine triphosphate (ATP) production. These beneficial effects work synergistically with calcium sensitization to improve myocardial performance. Phosphodiesterase inhibition leads to increased cAM*P* levels and augmented phosphorylation of phospholamban, and thus enhanced removal of cytosolic calcium by the sarcoplasmic-endoplasmic reticulum ATPase pump, resulting in accelerated relaxation of the myofilaments. Thus, we postulated that these positive biochemical effects of levosimendan can prevent postoperative atrial and/or ventricular arrhytmia after surgery in patients who undergo CABG.

The aim of the present prospective, blinded, randomized study was to evaluate the usefulness of levosimendan in preventing AF in patients with poor left ventricle function undergoing a first elective CABG. Here, we present the results of a pilot study designed to evaluate the effectiveness of perioperative and postoperative levosimendan administration and discuss possible strategies by which levosimendan treatment can be beneficial to prevent postoperative AF.

METHODS

Patient Selection

The study was approved by the ethics committee of the our institution, and written informed consent was obtained from each patient included in the study. In this prospective, double-blind, placebo-controlled, randomized study, patients received either levosimendan (n = 100) or placebo (500 ml saline solution, n = 100). All patients were undergoing isolated CABG. Patients with valvular disease, antiarrhythmic drug use, chronic renal failure, or chronic obstructive pulmonary disease were excluded from the study. Patients were also excluded if they had undergone any surgery, had suffered sustained ventricular tachyarrhythmia or cardiogenic shock, had undergone previous cardiac surgery, or had bradycardia (heart rate ≤55 bpm), significant alterations of atrioventricular conduction, sick sinus syndrome, permanent pacemakers, significant electrolyte disorders on admission, known thyroid disease, or abnormal liver function test results. Detailed physical examination, laboratory data with routine thyroid function tests, chest roentgenogram, and transthoracic echocardiography were performed routinely. The preoperative findings for patients in both groups are shown in Table 1.

Surgical Techniques

A median sternotomy was performed. Cardiopulmonary bypass was established by a regular cannulation technique with mild hypothermia (34°C). Myocardial protection was achieved with antegrade cold-blood cardioplegia (blood from the pump reservoir was mixed with crystalloid in a ratio of 4:1, which yielded a 21-mmol/L potassium concentration in the initial doses and 9 mmol/L in subsequent doses) given every 15 minutes antegradely immediately before release of the aortic cross-clamp. The left internal thoracic artery and saphenous veins were used as conduits for bypass grafting. Distal anastomoses were performed during a period of aortic cross-clamping, and proximal anastomoses were completed under partial aortic clamping during rewarming. At the end of the surgical

Table 1. Preoperative Characteristics of the Patients

Characteristic	Levosimendan Group (n = 100)	Control Group (n = 100)	*P*
Age, y	60.34 ± 1.53	60.92 ± 1.42	0.782
Male sex, n	60	54	0.547
Current smoker, n	45	56	0.690
Ejection fraction, %	26.30 ± 6.36	24.86 ± 1.08	0.234
EuroSCORE	7.06 ± 1.38	6.54 ± 0.15	0.543
Angina, n	54	60	0.064
Diabetes, n	42	44	0.841
Hypertension, n	70	58	0.214
Respiratory disease, n	19	16	0.337
Hypercholesterolemia, n	43	39	0.420
Preoperative MI,* n	15	20	0.785
Renal disease, n	10	7	0.956
PVD, n	20	25	0.82
Preoperative drugs, n			
-Blocker	47	45	0.803
Calcium channel blocker	24	29	0.564
ACE inhibitor	22	30	0.493
Nitrate	19	18	0.793
Left atrial dimension, mm	39.02 ± 3.64	35.38 ± 2.35	0.053
Preoperative arrhythmia, n	0	0	
Preoperative CRP levels, mg/L	1.30 ± 0.73	1.45 ± 0.66	0.43

*MI indicates myocardial infarction; PVD, peripheral vascular disease; ACE, angiotensin-converting enzyme.

procedure, patients were transferred to the intensive care unit (ICU). Patients were discharged from the ICU to the ward when their hemodynamic and respiratory condition was stable. The same medical staff performed all operations and anesthetic management throughout the study period.

Study Protocol

Levosimendan was started 6 hours before the operation in the ICU. In the operating room, the administration of levosimendan was continued at 24 µg/kg as a slow drip through the central venous catheter and stopped before the initiation of CPB. During the rewarming period, levosimendan was started again via the central vein with the same dose. If systolic blood pressure decreased by more than 20% compared with preinfusion values, for correction of mean arterial pressure volume loading was performed using a 500-mL Ringer's lactate solution. Control patients received a placebo (500 mL saline solution) infusion of equivalent volume over the same time interval.

Perioperative Measurement

Electrocardiograms (ECGs) and hemodynamic variables, including arterial blood pressure, heart rate, and central venous pressure, were monitored continuously throughout the operation and during the period in the ICU. After discharge from the ICU, all patients were monitored with an alarm-triggered telemetry system and double-checked for unnoticed events every morning for at least 5 postoperative days. A 12-lead ECG was obtained before surgery and on the first 5 postoperative days. Serum magnesium concentration was measured before surgery, immediately after surgery, and every morning for 5 days postoperatively and maintained at a level of >2.0 mEq/L. Serum potassium and calcium concentrations were also measured perioperatively and adjusted to maintain potassium levels at >4.2 mmol/L and calcium levels at>9.0 mg/dL. Cases were those patients who developed AF within 5 days after CABG surgery. AF was considered significant if it persisted for >30 minutes. All patients who had AF were treated according to protocol with intravenous (i.v.) amiodarone (bolus 5 mg/kg followed by an infusion of 15 mg/kg per 24 hours). Amiodarone oral treatment was also started in the 2.day after i.v. administration. High-sensitivity C-reactive protein (CRP) levels were measured before surgery and daily thereafter for 5 days postoperatively. CRP was determined by a nephelometric method.

Biological Markers

Because of the important effects of postoperative biological markers in CABG patients, such as cardiac enzymes, we have researched blood CRP levels, cardiac troponin I (TnI), and creatine kinase–MB (CK-MB) during the study period. Blood levels of TnI and CK-MB, as biochemical markers of cardiomyocyte injury, were serially measured by an immunoassay technique. Blood samples were obtained from peripheral vessels after the induction of anesthesia (baseline), on arrival in the ICU (postop 1), and at 6 h (postop 6), 24 h (postop 24), and 48 h (postop 48). The limits of quantification of cardiac TnI and CK-MB determination were as follows: 0.05 ng/mL and 6ng/mL, respectively. When values below the detection limit were reported, zero was used as the value.

Hemodynamic Monitoring

Hemodynamic monitoring consisted of heart rate, mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery wedge pressure, and cardiac output measurements. Derived cardiovascular variables, namely cardiac index and systemic vascular resistance index, were calculated using standard formulae. Output measurements were based on the bolus thermodilution technique, using the mean of 5 consecutive 5-ml injections of 5% glucose.

Statistical Analysis

Statistical analyses were performed with the SPSS for Windows 11.0 software system (SPSS Inc, Chicago, IL, USA). Variables were expressed as mean ± SD. Univariate analyses between groups were compared by t test, χ^2 test, and Fisher's exact test where appropriate. Univariate analysis of variance (ANOVA) and ANOVA with repeated measurements were used for the comparison of groups with regard to CRP, TnI, and CK-MB values. Binary logistic regression analysis with the backward Wald method was performed to determine the independent predictors of AF. Independent variables for the multivariate model were selected from those identified in a review of the literature. These variables were age and sex. Also included were variables that had an association of $P < 0.2$ with AF in the univariate model. A difference on a 2-tailed test was considered statistically significant for $P < 0.05$.

RESULTS

This randomized, prospective clinical trial was performed in 200 patients; 100 patients received levosimendan, and 100 received placebo. Statistically significant differences were not found for the variables of age, EuroSCORE (EUROpean System for Cardiac Operative Risk Evaluation), left ventricular ejection fraction, diabetes mellitus, hypertension, respiratory disease, preoperative myocardial infarction, or left atrial dimensions. In addition, there were no significant differences between groups in preoperative use of β-blockers, nitrates, calcium channel blockers, or angiotensin-converting enzyme inhibitors. Preoperative characteristics of the patients are summarized in Table 1.

Total inotropic drug requirements during the first 72 h after operation, plus postoperative electrocardiographic changes, complications, time on a ventilator, length of intensive care and hospital stay (ICU and hospital low-output syndrome) were recorded.

TnI and CK-MB release were significantly lower in the levosimendan group than in controls, while the peak value recorded 6 hours after surgery was also lower (for the changes of TnI blood levels, postop 1, $P = 0.026$; postop 6, $P = 0.005$; postop 24, $P = 0.044$; postop 48, $P = 0.006$ [Mann–Whitney nonparametric sum rank test]). The mean hospitalization time was approximately doubled in the control group. In these patients we detected long AF durations and episodes during the clinical follow-up.

Table 2. Operative and Postoperative Characteristics.

Characteristic	Levosimendan Group (n = 100)	Control Group (n = 100)	*P*
Operation time, min	144.2 ± 6.90	156.4 ± 7.08	0.972
Bypass time, min	66.10 ± 2.90	61.40 ± 1.80	0.193
Cross-clamp time, min	32.03 ± 7.22	35.10 ± 10.2	0.269
LIMA* used, n	100	100	1.00
Grafts per patients	3.43 ± 0.11	3.07 ± 0.12	0.354
Intraoperative defibrillation, n	18	23	0.001
Perioperative infarction, n	4	3	1.00
Operative mortality, n	0	0	
Postoperative AF, n	12	36	0.005
Inotropic agent use, n	10	14	0.185
Hospital stay, d	5.34 ± 0.717	11.20 ± 1.22	0.0001
MBP during rewarming, mm Hg	66.0 ± 3.2	61.1 ± 4.6	0.658
Mean CVP after bypass, mm Hg	2.4 ± 1.4	2.5 ± 1.5	0.768
Heart rate after bypass until onset of AF, bpm	79.6 ± 4.8	83.8 ± 2.6	0.298

*LIMA indicates left internal mammary artery; MBP, mean blood pressure.

Operative Characteristics

Among the operative characteristics (Table 2), the differences between bypass times and cross-clamp times were not significant. In all patients, the left internal mammary artery was used with an in situ technique. After release of the aortic clamp, defibrillation of the heart was necessary in 9 patients in the levosimendan group and 24 in the control group ($P = 0.001$).

Postoperative Characteristics

The physicians and nurses in the ICU were blinded to the group status of patients in the levosimendan and control groups. There were no perioperative myocardial infarctions or in-hospital deaths in either group. More patients in the levosimendan group were free of inotrope use than in the control group, and the period of inotropic medication use was also shorter in the levosimendan group, but these differences did not reach statistical significance. Intraaortic balloon pumps were not required in any of the patients. Patients were weaned from mechanical ventilation when they were hemodynamically stable, responded to verbal stimulation, and were completely rewarmed and when blood loss did not exceed 100 mL/h. Cardiovascular and respiratory values and temperatures were recorded every 15 minutes before extubation and then hourly until discharge from the ICU. Patients were discharged from the ICU on the first morning that they were hemodynamically stable, had normal blood gases during spontaneous breathing, and had satisfactory renal function. The length of stay in the ICU was similar in both groups ($P = 0.654$). The mean hospital stay was significantly lower in the levosimendan arm than in the control arm of the study (Table 2).

Postoperative AF

During the study period, 36 patients in the control group (36%) developed postoperative AF, whereas 12 (12%) of the levosimendan patients developed AF ($P = 0.005$). AF occurred a mean of 3.66 ± 1.52 days after surgery in the levosimendan group and 3.55 ± 0.51 days after surgery in the control group ($P = 0.650$). There was a significant difference between groups in the duration of AF (3.40 ± 1.86 versus 6.50 ± 1.94 hours, $P = 0.021$).

In the levosimendan group, we detected 2 AF episodes in only 2 patients (16%). In the control group, recurrent AF episodes were detected in 8 patients (22%). This was statistically not significant ($P > 0.05$). In the remaining patients in the levosimendan group, AF episodes were not detected. Sinus rhythm was restored in the levosimendan group and in the control group.

Electrical cardioversion was not performed on any patient in either group. There were no statistically significant differences in any variables between patients who experienced postoperative AF and those who did not (Table 3). Baseline CRP levels were similar in the levosimendan and control groups. During the study, the average level of postoperative CRP in both groups increased, with a peak concentration on the second day. Elevated CRP levels decreased and did not return to normal levels by day 4 in either group. When preoperative and operative variables were included in the multivariate analysis, levosimendan (odds ratio [OR] 3.220, 95% confidence interval [CI] 1.450 to 9.200; $P = 0.006$) and age (OR 2.049, 95% CI 0.760 to 1.560; $P = 0.059$) were the only independent predictors of postoperative AF.

Table 3. Changes of Blood CRP Levels in the Control Group and the Levosimendan Group.*

Control Group				
Time Point	No AF (n = 64)	AF (n = 36)	*P* within Group	
Preoperative	1.4 ± 0.4	1.2 ± 0.1	NS	
Postoperative day 1	42.5 ± 10.5	49.1 ± 6.4	NS	
Postoperative day 2	49.10 ± 5.6	48.3 ± 9.2	NS	
Postoperative day 3	42.40 ± 7.0	44.3 ± 3.3	NS	
Postoperative day 4	36.0 ± 6.9	35.4 ± 4.8	NS	
Postoperative day 5	13.25 ± 3.8	11.7 ± 2.2	NS	
Levosimendan Group				
Time Point	No AF (n = 12)	AF (n = 88)	*P* within Group	*P* between Groups
Preoperative	1.5 ± 0.7	1.2 ± 0.3	NS	0.46
Postoperative day 1	31.7 ± 9.5	32.1 ± 8.4	NS	<0.05
Postoperative day 2	33.1 ± 2.6	37.30 ± 8.2	NS	<0.05
Postoperative day 3	32.46 ± 6.0	35.3 ± 5.3	NS	<0.05
Postoperative day 4	25.5 ± 6.0	24.4 ± 5.8	NS	<0.05
Postoperative day 5	8.6 ± 2.8	8.9 ± 1.2	NS	<0.05

*Statistical comparison of CRP levels shows no difference within groups. However, when we compared the change of CRP levels, we found statistical differences between the groups.

DISCUSSION

In spite of the development in extracorporeal circulation and surgical techniques, the frequency of postoperative AF remains high. AF and/or flutter is the most common arrhythmia developed after CABG. AF is often a short-lived but it is associated with significant morbidity. Several factors may contribute to the development of AF after cardiac surgery. Operative trauma, rise in atrial pressure due to postoperative ventricular stunning, increase of atrial electrical susceptibility from rapid return of temperature after cardioplegic arrest, atrial distention by fluid overload, chemical stimulation during infusion of inotropic drugs, reflex sympathetic activation, and pericardial or respiratory complications [Svedjeholm 2000; Allesie 2001; Hakala 2002; Aviles 2003]. Cardiac overload can result in decreased resting potential and the occurrence of depolarizations that cause extra systoles that originate in the region of greatest stretch [Allesie 2001].

The efficacy of pharmacological prophylaxis in reducing the incidence of AF has been researched previously. The authors have demonstrated the efficacy of amiodarone in decreasing the incidence of postoperative AF [Daoud 1997; Redle 1999; Treggiari-Venzi 2000; Budeus 2006]. There have been different studies for prevention of post-CABG AF with digoxin, β-blockers, magnesium, or a combination of these drugs [Gomes 1999; Solomon 2000; Tokmakoglu 2002]. Aerra and colleagues [Aerra 2006] showed that the combination of sotalol and magnesium can significantly reduce the incidence of postoperative AF. Recent data have suggested a possible protective role of statins [Patti 2006] and steroids [Prasongsukarn 2005].

Massoudy et al. [Massoudy 1999] reported that administration of nitroprusside (as an NO donor) for just the first 20 minutes of reperfusion to patients undergoing CABG led to a reduction of the acute inflammatory response, especially a reduction in levels of interleukin-6 and interleukin-8.

The recent upsurge in referral for cardiac surgery of patients with high perioperative risk or compromised left ventricular function has lead to an increasing use of pharmacologic support in the form of vasodilator and inotropic therapy to achieve improvement of tissue perfusion in the perioperative period or to support weaning from cardiopulmonary bypass. Traditionally, perioperatively used inotropic agents, such as epinephrine, dobutamine, and milrinone, are limited by significant increases in myocardial oxygen consumption, proarrhythmia, or neurohormonal activation.

Levosimendan, a new inodilator for the treatment of decompensated heart failure, has also shown promise in elective therapy of cardiac surgical patients with high perioperative risk or compromised left ventricular function, as well as in rescue therapy of patients with difficult weaning from cardiopulmonary bypass. In this article we briefly discusses the pharmacology of levosimendan and evaluate the current best available evidence to assess the safety and efficacy of levosimendan usage in cardiac surgery.

Levosimendan, a pyridazinone-dinitrite and a member of a new class of agents, the calcium sensitizers, that increase myocardial contractility without increasing intracellular calcium, has emerged as an inotropic agent [Figgitt 2001; Lehtonen 2001; Frishman 2003]. In preclinical and clinical studies, levosimendan has been shown to exert potent dose-dependent positive inotropic and vasodilatory activity

Table 4. Comparison of All Patients with and without AF.

Patient Characteristic	With AF (n = 48)	Without AF (n = 152)	*P*
Male sex, %	52.5	61.8	0.1
Age, y	64.08 ± 10.98	59.53 ± 10.05	0.062
Preoperative drugs, %			
β-Blockers	72	73	1.000
Calcium antagonists	19.0	28	0.401
Preoperative LVEF,* %	25.20 ± 7.24	23.0 ± 9.5	0.831
Preoperative MI, %	83	73	0.419
Diabetes mellitus, %	45.4	42.1	0.815
Hypertension, %	56.7	53.2	0.812
Angina, %	58.8	64.5	0.469
Renal disease, %	35.0	29.8	0.363
Peripheral vascular disease, %	41.5	36.3	0.202
Smoker, %	42.9	44.7	0.168
No. of distal anastomosis	2.54 ± 0.8	2.53 ± 0.7	0.991
LIMA used, %	100	100	
Intraoperative defibrillation, %	28.8	23.9	0.141
Operation time, min	140.41 ± 12.39	145.47 ± 39.98	0.449
Cross-clamp time, min	34.75 ± 9.82	37.10 ± 15.97	0.294
Bypass time, min	63.41 ± 9.76	69.55 ± 21.50	0.256
Inotrope used, %	24.2	14.5	0.284

*LVEF indicates left ventricular ejection fraction; MI, myocardial infarction; LIMA, left internal mammary artery.

and has emerged as a promising alternative to conventional inotropic agents for patients with heart failure. In this study, we researched the efficacy of antiarrhytmic pharmacologic effects of levosimendan on the basis of clinical data and on the safety of levosimendan usage in CABG patients.

In our patients, the mean hospitalization time was approximately doubled in the control group. As we known that cardiac troponin displayed powerful prognostic properties in patients with AF, with almost a 2-fold increase of stroke risk and more than a 3-fold increase of cardiovascular mortality when AF patients had elevated versus undetectable levels were compared. Leal et al have shown that the higher cTnI serum levels were detected in patients who developed AF at the postoperative period after CABG [Leal 2012]. Thus, when we detected high cardiac biomarkers such as cardiac TnI and CK-MB after CABG, we followed the patients for a long time after discharge from the hospital. The properties of cardiac troponin as a risk predictor in AF have subsequently been described in an outpatient AF cohort [Roldan 2012].

The clinical observations of the present study suggest that levosimendan decreases AF after CABG. The protocol tested in the present study, in which patients without a history of atrial arrhythmias were given levosimendan, has demonstrated a clinical benefit, with a reduction of postoperative AF and a significant reduction in length of hospital stay in our CABG patients. Additionally, AF duration was significantly lower in the levosimendan group, thus decreasing the length of hospitalization, which has important clinical and economic implications.

The mechanism involved in the levosimendan effect of suppression of postoperative AF is not clear. Several underlying mechanisms can explain this effect. We known that levosimendan use in cardiac surgery provides myocardial preconditioning and vasodilating effects without intracellular calcium accumulation during the ischemia-reperfusion injury. Levosimendan offers the advantage of increasing systolic force without compromising coronary perfusion, due in part to a synergistic mechanism of action attributed to opening of the

adenosine triphosphate–sensitive potassium channels [Figgitt 2001; Lehtonen 2001; Sorsa 2001; Frishman 2003]. The opening of ATP–sensitive potassium channels by AT*P* produces peripheral vasodilation, coronary artery dilation, and myocyte mitochondrial activation [McBride 2003].

In vitro studies have consistently demonstrated that positive lusitropic effects can be attributed to phosphodiesterase III inhibition at higher concentrations [Lehtonen 2001]. Phosphodiesterase inhibition leads to increased cAM*P* levels and augmented phosphorylation of phospholamban, and thus enhanced removal of cytosolic calcium by the sarcoplasmic-endoplasmic reticulum ATPase pump, resulting in accelerated relaxation of the myofilaments. Levosimendan-induced inhibition of the L-type calcium current by cGM*P* mechanisms leads to less activation of the calcium-induced calcium release process, thereby reducing atrial contractility and, consequently, energy consumption. It is also of benefit in the setting of pulmonary vasoconstriction and right ventricular dysfunction. In an experimental setup, the drug has been shown to increase ventricular contractility and hydraulic power without changing pulmonary vascular resistance [Leather 2003]. In patients with heart failure, the drug has been shown to reduce pulmonary vascular resistance [Nieminen 2000; Slawsky 2000].

The potential role of inflammation in the pathogenesis of post-CABG AF has been proposed with some supporting data. Bruins et al [Bruins 1997] were the first to propose the inflammation-AF hypothesis, after their observations of an increased frequency of AF after CABG.

In our present clinical observations, serum CRP concentration increased markedly in the postoperative period in both groups; however, CRP concentrations were reduced significantly in the levosimendan group during the postoperative period. This appears to support the idea that a higher concentration of CRP is an important factor in the development of postoperative AF; however, the present study did not show any statistically significant within-group association of CRP levels in the AF-positive and AF-negative groups, nor was the study sufficiently powered to evaluate the role of other predictors of AF.

In conclusion, the present study shows that pretreatment with levosimendan and continued use during the rewarming period significantly decreases the incidence and duration of postoperative AF after CABG. Levosimendan is also well tolerated and does not increase the incidence of perioperative complications.

Limitations of Available Evidence

Experience with levosimendan use is limited in CABG patients. Although hemodynamic efficacy has been established in the perioperative period, levosimendan has been studied only as a short-term therapy, generally infused for 6 to 24 hours in our patients. There is nothing in the literature to suggest an optimum duration of therapy. Furthermore, data for determination of an optimum dosage also are limited. Beneficial hemodynamic effects are dose dependent; however, so are most of the adverse effects. Based on available information it can be recommended that a lower dosage regimen (bolus < 36 µg/kg/min and infusion <0.4 µ/kg/min) seems to be safe and effective for these patients. Finally, no data are available at present to validate the long-term safety of levosimendan, necessitating mandatory ECG monitoring to detect QT prolongation and ventricular arrhythmias.

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