Comparison between the level of interleukin-6 and B-type natriuretic peptide as predictors of the outcome after coronary artery bypass graft surgery

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Introduction

The B-type natriuretic peptide (BNP) and interleukin-6 (IL-6) are increasingly being used as biomarkers for the diagnosis, management, and prognosis of complications after cardiac surgery with cardiopulmonary bypass (CPB). The aim of this study was to assess preoperative and postoperative levels of BNP and IL-6 in patients undergoing coronary artery graft surgery (CABG) with CPB and investigate their variation and ability to correlate with immediate postoperative outcome.

Patients and Methods

Patients scheduled for elective CABG with CPB were enrolled in this study. Plasma levels of BNP and IL-6 were measured preoperatively, 6, 12, and 24 h after CPB. The main endpoints were the correlation between the level of BNP and IL-6 and the requirements for an intra-aortic balloon pump, artificial ventilation for more than 24 h, intensive care unit (ICU) stay longer than 5 days, requirement for inotropic support, hospital stay, and clinical complications (infection, myocardial infarction, ventricular arrhythmias, stroke, or renal failure).

Results

Sixty-eight patients (eight women and 60 men), median age 63.3 ± 6.9 years, were included in the study. Preoperative BNP levels correlated with longer ICU stay ($P = 0.003$), longer mechanical ventilation ($P = 0.016$), and longer epinephrine and milrinone use ($P < 0.001$), whereas BNP at 24 h after CABG correlated only with longer epinephrine and milrinone use ($r = 0.418$, $P = 0.003$). Preoperatively and 6 h postoperatively, IL-6 correlated with longer epinephrine and milrinone use ($P = 0.018$) and longer ICU stay, and was significantly increased in patients with infection at all time points of measurement.

Conclusion

BNP correlates with clinical endpoints more than IL-6 and both can be used together as predictors of early outcome after coronary artery bypass grafting surgery.

Keywords:
B-type natriuretic peptide, coronary artery graft surgery, interleukin-6

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Introduction

Various clinical, laboratorial, and hemodynamic factors have been used to assess the preoperative and postoperative risks for patients with ischemic heart disease undergoing coronary artery graft surgery (CABG) [1]. Thus, there remains an important need to identify modifiable perioperative risk factors that associate strongly with the postoperative outcomes that adversely impact both poor health-related quality of life and survival after CABG surgery [2]. Biomarker analyses play a role in providing independent prognostic information in these patients [3]. For a biomarker to be clinically useful in the perioperative setting, it should be easy to measure, sensitive and specific for the outcome of interest, and add to what a clinician already knows from clinical experience and available and less expensive tests [4]. An inflammatory response after cardiopulmonary bypass (CPB) is associated with systemic release of tumor necrosis factor and interleukin-6 (IL-6) [5]. There is accumulating evidence that the inflammatory status plays an important role in the development of left ventricle (LV) remodeling including structural and functional changes of the myocardium and heart failure after cardiac surgery [6]. IL-6 is a multifunction, proinflammatory cytokine that is chronically increased in both heart disease and certain psychiatric disorders, such as depression, and common comorbidities with heart diseases [7–10]. IL-6 was proposed as a biomarker of cardiac disease severity, given its link with myocardial gene expression [10] and its direct association with myocardial injury [11].

Moreover, plasma B-type natriuretic peptide (BNP) is an established diagnostic and prognostic biomarker in ambulatory heart failure (HF) and acute coronary syndrome patients [12]. BNP is secreted primarily by cardiac ventricular myocytes in response to ventricular pressure and volume overload and ischemia [13].

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It has been shown that increased preoperative and peak postoperative BNP associate independently with longer postoperative hospital stays and early cardiac ventricular dysfunction, as well as longer-term decreased physical functioning and all-cause mortality after primary CABG surgery [14]. Therefore, we carried out this study to compare perioperative BNP and IL-6 levels and the outcome of patients with coronary heart disease subjected to an elective primary CABG.

Patients and Methods

Sixty-eight patients, aged 20–75 years, scheduled for isolated primary CABG surgery with CPB, were enrolled prospectively in this study in Dr Erfan General Hospital, Jeddah, Saudi Arabia. Respective institutional review board approval and written informed consent were obtained from all the patients.

Exclusion criteria included age older than 75 years, concomitant inflammatory and consumptive disease, acute infection, collagen disorders, a preoperative hematocrit less than 25% or transfusion of leukocyte-rich blood products within 30 days before surgery, previous cardiac surgery, symptomatic heart failure, emergency surgery or concurrent valve surgery, CABG surgery without CPB or without an aortic cross-clamp, if they received a preoperative inotrope, an intra-aortic balloon pump (IABP), or ventricular assist device support, and severe renal dysfunction (requiring preoperative hemodialysis or with preoperative serum creatinine >3 mg/dl, severe renal dysfunction and perioperative dialysis can influence plasma BNP concentrations variably) [12].

All patients were subjected preoperatively to comprehensive echocardiography (EnVisor C Ultrasound System; Philips Medical Systems, Eindhoven, the Netherlands) carried out by the echocardiography team in our institute. Measurements included interventricular septal thickness, posterior wall thickness, LV diameter at end-diastole, and right ventricular diameter at end-diastole. LV ejection fraction (EF) was calculated according to the Teichholz equations [15]. Echocardiography was repeated when clinically indicated and in all patients on the 7th day after CABG.

Data collection

At baseline, demographic data (age, sex) and history of conventional vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking habit, alcohol abuse), and of atrial fibrillation, chronic obstructive pulmonary disease, and chronic kidney disease were obtained. Patient records were evaluated, and past medical and surgical histories were determined by previous records. LVEF was evaluated by echocardiogram. Cardiac catheterization data were assessed as indicated by the attending cardiologist, independent of the study. Routine laboratory investigations were performed on the first day after admission to the hospital after overnight fasting, and included levels of glucose, total cholesterol, HDL-cholesterol, triglycerides, urea, creatinine, uric acid, fibrinogen, hemoglobin, and hematocrit. Peripheral venous blood samples (10 ml) were obtained from patients preoperatively, 6, 12, and 24 h after CPB. Samples were collected into a tube containing potassium EDTA, which was used as an anticoagulant. All serum samples for each individual were stored at −70°C for subsequent enzyme-linked immunosorbent assays (ELISA). BNP levels were determined using sandwich immunoassays on a Triage platform (Biosite, San Diego, California, USA), and the normal values of BNP were <100 pg/ml. Commercial ELISA detection of cytokines IL-6 was used. Measurements were performed in duplicate, at the same time by the same ELISA, to avoid variation in assay conditions. Normal values for IL-6 were 3.12 pg/ml.

Anesthetic and cardiac procedure

General anesthesia was induced with etomidate (0.2 mg/kg), fentanyl 5 μg/kg, and pancuronium 0.1 mg/kg. Anesthesia was maintained with an infusion of fentanyl 5–10 μg/kg/h, pancuronium 0.03 mg/kg, and 2% end-tidal sevofloran. All patients were ventilated with an oxygen–air mixture (FiO_2: 0.5) to maintain an end-tidal PCO_2 of 35–45 mmHg. After orotracheal intubation, a three-lumen central venous catheter (Arrow, Reading, Pennsylvania, USA) was inserted into the right internal jugular vein.

Before CPB, heparin 350 U/kg and additional boluses of 50 U/kg were administered to maintain an activated clotting time of at least 480 s. Normothermic CPB was performed using a membrane oxygenator and a centrifugal pump was adjusted to a cardiac index of 3 l/min/m^2. Warm blood cardioplegia was used. On-pump CABG was carried out with normothermic (37°C) CPB using intermittent antegrade hyperkalemic warm blood cardioplegia supplemented with magnesium (which is the standard technique used in our instate) [16].

Clinical postoperative events

From the outcome data, clinical events were defined as follows: postoperative ventricular dysfunction was defined as a new requirement for two or more inotropes or as a new placement of an IABP or a ventricular assist device either during the intraoperative period after the patient separated from CPB or postoperatively in the intensive care unit. New-onset postoperative atrial fibrillation was defined as the occurrence of atrial fibrillation postoperatively in patients who did not present for surgery in atrial fibrillation. Inotrope support was defined as a continuous infusion of amrinone, milrinone, dobutamine, dopamine at least 5 μg/kg/min, epinephrine, isoproterenol, norepinephrine, or vasopressin, ICU stay longer than 5 days, ventilator dependence more than 24 h, hospital stay more than 10 days, clinical complications (infection, myocardial infarction, renal failure, stroke, and ventricular arrhythmias), and inhospital mortality. The diagnosis of myocardial infarction was made on the basis of ECG changes (new persistent Q waves and ST segment deviations: 1 mV ST segment increases in ≥2 limb leads, and/or 2 mV ST segment increases in ≥2 precordial leads), and an increase in serum creatine kinase-MB levels 10 times beyond the upper limit of normal range. We also analyzed the correlation of the markers with these events for all patients and separately for patients with preserved LVEF (>0.40) and for patients with impaired LVEF (<0.40).

Statistical analysis

All data were analyzed using the statistical package SPSS (version 10.0; SPSS Inc., Chicago, Illinois, USA) and R (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria). *P*-values for all study analyses were two tailed. Continuous data are presented as mean ± SD and categorical data as absolute numbers and percentages.

The Wilcoxon signed-rank test was used to compare differences in BNP and IL-6 concentration at the different study time points. The Wilcoxon rank sum test was used to carry out between-group comparisons of BNP and IL-6 levels were measured at each time point. Wilcoxon signed-rank tests were used to compare BNP versus IL-6 concentrations in the group of patients who experienced a postoperative event and in the group of patients who did not experience a postoperative event. The Mann – Whitney test was used for a comparison of clinical variables between preserved and impaired LVEF patients. The utility of markers and EF in predicting postoperative complications was evaluated using receiver-operating characteristic curves. A *P*-value less than 0.05 was considered statistically significant.

Results

Seventy-two patients scheduled for elective on-pump CABG were enrolled in this study. Four patients were excluded on the basis of the exclusion criteria. Thus, 68 patients (eight women and 60 men), median age 63.3 ± 6.9 years, were included in the study. All patients were asymptomatic for heart failure, had hemodynamic stability, and needed no oxygen support before surgery. Twenty-four patients showed good preoperative left ventricular systolic function (EF^{3}40%), whereas the rest of the patients (44) presented with variant degrees of decreased left ventricular systolic function (EF ≤40%). Table 1 shows the clinical and surgical characteristics of the 68 patients included in the study analysis. The mean patient age was 64.2 ± 6.9 years. For 60 men (88.24%) and eight women (11.76%), intraoperative and postoperative data, cardiac events, and the clinical endpoints are shown in Table 2. The mean number of bypass grafts was 2.23 ± 0.75. Milrinone and/or epinephrine were infused in almost half of the patients in the study group.

Table 1 Demographic,clinical, and surgical characteristics of the study population

Age (years) (mean ± SD)	64.2 ± 6.9
Creatinine (mg/dl) (mean ± SD)	1.14 ± 0.15
Urea (mg/dl) (mean ± SD)	48.0 ± 25.5
Number of grafts (mean ± SD)	2.23 ± 0.75
CPB duration (min) (mean ± SD)	85.66 ± 15.32
Duration of surgery (min) (mean ± SD)	352.9 ± 72.8
Number of the grafts (mean ± SD)	2.4 ± 1.6
Males [*n* (%)]	60 (88.24)
Females [*n* (%)]	8 (11.76)
LVEF >40% [*n* (%)]	24 (35.3)
LVEF <40% [*n* (%)]	44 (64.7)
Smoking history [*n* (%)]	25 (36)
Hypertension [*n* (%)]	58 (85.2)
Diabetes mellitus [*n* (%)]	52 (76.4)

CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction.

Table 2 Clinical endpoints

Epinephrine (patients) [*n* (%)]	10 (14.7)
Milrinone (patients) [*n* (%)]	55 (80.8)
IABP [*n* (%)]	4 (5.8)
Postoperative mechanical ventilation duration (min) (mean ± SD)	521.4 ± 198.16
Inhospital stay after surgery (days) (mean ± SD)	13.1 ± 10.5
Intensive care unit stay >5 days [*n* (%)]	8 (11.7)
Mortality in the ICU [*n* (%)]	3 (4.4)
Myocardial infarction [*n* (%)]	2 (2.9)
Postoperative infection [*n* (%)]	6 (8.8)
Dialytic renal failure [*n* (%)]	1 (1.4)
Stroke [*n* (%)]	1 (1.4)
Hospital mortality [*n* (%)]	1 (1.4)

IABP, intra-aortic balloon pump.

On postoperative subgroup analysis, patients with LVEF up to 0.40 required more milrinone and epinephrine infusion ($P < 0.001$), had longer ventilator dependence ($P < 0.001$), and longer ICU stay ($P < 0.001$) than patients with LVEF at least 0.40. After surgery, 10 patients developed a moderate infection with a median onset on day 4 (range, 2–7) after surgery. The infections were gram-negative in six cases (60%), gram-positive in four cases (40%), and fungal in two cases (20%) as some patients had more than one organism. In two patients, no infectious agent could be isolated. Seven patients (70%) developed postoperative pneumonia, three patients (30%) developed wound infections, and three patients (30%) developed catheter infection as some patients had more than one infection. Three patients (30%) developed sepsis. Fifty-eight patients did not develop postoperative infections.

Postoperative plasma BNP concentrations were all significantly increased compared with the preoperative plasma BNP concentration ($P < 0.0001$). Preoperative plasma BNP measurements were associated significantly with peak postoperative plasma BNP ($P < 0.0001$). The median peak postoperative BNP concentration after 6 h was 168.44 ± 241.45 pg/ml. The mean peak 24 h postoperative BNP was 227.95 ± 245.65 pg/ml. Plasma BNP levels increased consecutively and significantly postoperatively ($P < 0.0001$). However, the IL-6 level was 9.79 ± 16.72 preoperatively and increased significantly to 227.95 ± 245.65 after 24 postoperatively ($P < 0.0001$).

Statistical analysis using the Mann – Whitney and Spearman test verified the correlation of each marker with clinical events and is briefly described as follows: the levels of each marker are shown in Table 3. Preoperative BNP levels correlated with longer ICU stay Fig. 1 ($r = 0.356$, $P = 0.003$), longer mechanical ventilation ($r = 0.244$, $P = 0.016$), and longer epinephrine and milrinone use ($r = 0.612$, $P < 0.001$) Fig. 2. BNP also at 6 h after CABG correlated with longer ICU stay ($r = 0.246$, $P = 0.029$), longer need for mechanical ventilation ($r = 0.268$, $P = 0.038$), and longer epinephrine and milrinone use ($r = 0.523$, $P < 0.001$). BNP at 24 h after CABG correlated only with longer epinephrine and milrinone use ($r = 0.418$, $P = 0.003$).

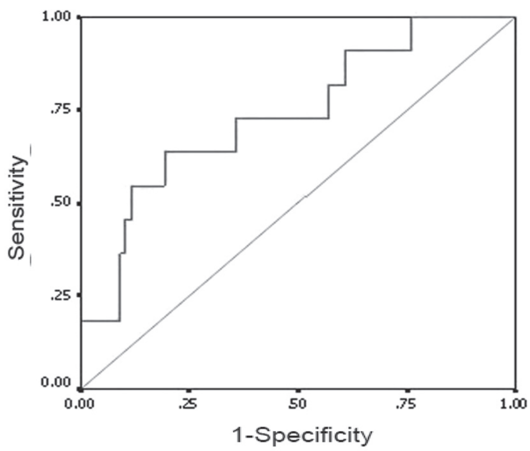
Preoperatively, IL-6 correlated with longer epinephrine and milrinone use ($r = 0.299$, $P = 0.018$). At 6 h after CABG, IL-6 did not correlate with events. IL-6 at 24 h after CABG correlated with longer epinephrine and milrinone use ($r = 0.344$, $P = 0.003$) and with postoperative infection ($r = 0.391$, $P = 0.004$). Furthermore, IL-6 was significantly increased in patients with infection at all time points of measurement (Fig. 3).

Discussion

An extensive number of investigations have been carried out in an attempt to predict postoperative morbidity and mortality in patients undergoing coronary revascularization as the variations in recovery time, complications, and survival among cardiac patients who have undergone CABG procedures are vast. Many formulas and theories are used to predict clinical outcome and recovery time, and current prognostic predictions are based on medical and family history, lifestyle, comorbidities, and performance status.

The identification of biomarkers that provide concrete evidence supporting clinical outcome has markedly

Figure 1



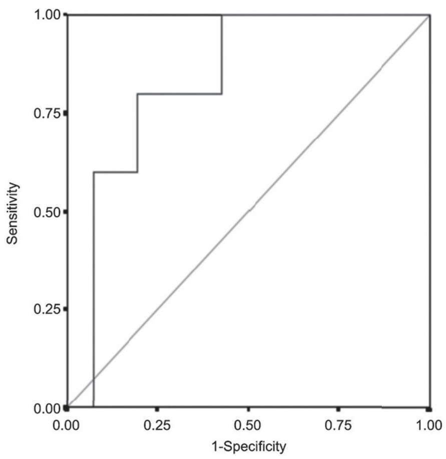
Receiver operator characteristic curve (ROC) for preoperative BNP levels and the need for epinephrine and milrinone infusion. BNP level greater than 58.4 pg/ml correlated with the use of epinephrine and milrinone (sensibility = 77.2%, specificity = 74.3%, accuracy = 76.5%, odds ratio = 10.5, positive predictive value = 88.9%, negative predictive value = 9.09%), with an area under the curve of 0.822. BNP, B-type natriuretic peptide.

Table 3 Marker levels preoperatively, and 6 and 24 h postoperatively

	Preoperative	6 h	24 h	*P*-value	
				Preoperative-6 h	Preoperative-24 h
IL-6 (pg/ml)	9.79 ± 16.72	73.59 ± 69.34	38.23 ± 49.34	$P < 0.001$	$P < 0.001$
BNP (pg/ml)	126.08 ± 165.35	168.44 ± 241.45	227.95 ± 245.65	NS	$P < 0.001$

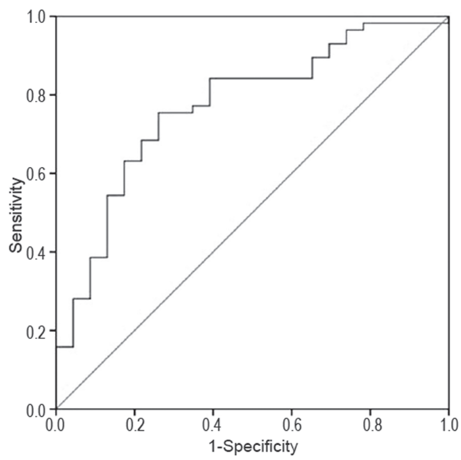
BNP, B natriuretic peptide; IL-6, interleukin-6; NS, nonsignificant; preoperative-6 h, variation before and 6 h after cardiopulmonary bypass; preoperative-24 h, variation before and 24 h after cardiopulmonary bypass.

Figure 2



Receiver operator characteristic curve (ROC) for preoperative BNP levels predicting intensive care unit (ICU stay >5 days). BNP level greater than 190 pg/ml was a strong predictor of ICU stay more than 5 days, with an area under the curve of 0.708 (sensibility = 62%, specificity = 83.6%, accuracy = 81.4%, odds ratio = 8.4, positive predictive value = 26%, negative predictive value = 96.8%). BNP, B-type natriuretic peptide.

Figure 3



Receiver operator characteristic curve (ROC) for preoperative IL-6 levels predicting postoperative infection. ROC curve for preoperative IL-6 levels and the postoperative infection, with an area under the curve of 0.702. IL-6, interleukin-6.

affected the field of medicine, helping clinicians in many medicine subspecialties to predict clinical course. However, very few studies have evaluated the behavior of these markers before and after CABG with CPB, their curves, and correlation with clinical events.

For a biomarker to be clinically useful in the perioperative setting, it should be easy to measure, sensitive and specific for the outcome of interest, and add to what a clinician already knows from clinical experience and available and less expensive tests [4].

BNP is secreted primarily by cardiac ventricular myocytes in response to increased ventricular wall stress induced by volume or pressure overload or ischemia. Several studies have been published expressing BNP as an important predictor for patients with heart failure under clinical treatment. However, only a few studies have verified preoperative BNP as a predictor for outcome in cardiac surgery [17,18].

However, IL-6 is a multifunction, proinflammatory cytokine that is chronically increased in both heart disease and certain psychiatric disorders, such as depression, commonly comorbid with heart diseases [8,19]. IL-6 was proposed as a biomarker of cardiac disease severity, given its link with excess preoperative IL-6 levels; however, it may impact the heart directly. Higher levels have been linked with immediate postoperative heart dysfunction [20,21].

In the current study, we aimed to compare between preoperative and postoperative levels of BNP and IL-6 and their correlation with the outcome after CABG.

We hypothesized that in patients with known preoperative coronary artery disease presenting for primary CABG surgery, increased preoperative and peak postoperative BNP and IL-6 concentrations are associated significantly with the occurrence of postoperative complications.

Our study found that preoperative and 6 h post-CABG BNP levels correlated with longer ICU stay, longer mechanical ventilation, and longer cardiac support medication use, whereas BNP at 24 h after CABG correlated only with longer inotrope use. These results are in agreement with the study carried out by Hutfless *et al.* [22], who observed that preoperative BNP is associated with longer inhospital stay, IABP requirement, and 1-year mortality, independent of LVEF.

Our study indicates that preoperative BNP cut-off levels greater than 190 pg/ml may predict longer ICU stay among stable patients undergoing heart surgery. Although this level of BNP is higher than the cut-point of 100 pg/ml that was used by Maisel *et al.* [23] for making the diagnosis of congestive HF it is less than the cut-point reported by Harrison *et al.* [24], who found that BNP levels above 480 pg/ml could predict future congestive HF events in patients presenting with dyspnea to the emergency department (480 pg/ml).

It should be noted that preoperative BNP, despite high specificity and accuracy, had low sensitivity and positive predictive value in our study. This suggests that BNP levels are best used not as a 'stand-alone' test, but in conjunction with existing multivariable risk indexes or to be used with another biomarker such as IL-6.

It has been shown that patients with cardiogenic shock show similarly high IL-6 levels as in patients with septic shock [25]. In the setting of acute myocardial infarction, IL-6 was identified as an independent prognostic marker [26].

Our study showed that preoperatively, IL-6 correlated with longer epinephrine and milrinone use and was significantly increased in patients with postoperative infection at all time points of measurement. The site of infection was pulmonary in most cases. Thus, patients with an infection were mechanically ventilated significantly longer than patients without infection. This was also associated with a significant increase in the length of ICU treatment.

Furthermore, IL-6 peaked immediately after surgery. Increased IL-6 in patients with postoperative infection suggests more severe tissue trauma in these patients [27]. This may cause disruption of the physiologic cytokine pattern, leaving the patient at risk of postoperative infection.

Our finding is in agreement with the study carried out by Andrié *et al.* [28], who showed the link between postoperative plasma IL-6 and length of hospital stay, and the study carried out by Amy L, who assumed IL-6 to be the strongest independent predictor of 30-day mortality after cardiac surgery [29].

Our study was limited to a single-site convenience sample and a relatively small sample size, and thus does not allow strong conclusions. Although we cannot establish a cut-off value for complications, preoperative BNP greater than 190 pg/ml correlated with longer ICU stay with considerable accuracy. The limited numbers did not allow us to analyze the data in a multivariate manner, specifically with the inclusion of CPB and cross-clamp times. Nevertheless, we cannot exclude that some patients were at a higher risk of subsequent onset of infection as a result of their increased blood glucose levels, which was not included in our data analysis for correlation with postoperative infection. Future studies are needed to describe cardiac structural changes that may exist preoperatively or occur over time in CABG patients, who have increased perioperative BNP or IL-6 concentrations. Such future studies should incorporate detailed echocardiographic characterization of cardiac structure and function, with a corresponding delineation of the correlations between these echocardiographic assessments and perioperative and longer-term postoperative BNP concentrations.

Conclusion

BNP has considerable predictive value for postoperative complications in patients with coronary artery disease undergoing CABG more than IL-6, whereas increased IL-6 after CPB is predictive of postoperative infection and longer ICU stay.

Our results also suggest that it may be judicious to more closely monitor patients with higher BNP and IL-6 levels for possible postoperative complications.

Future studies are warranted to assess whether medical management, to reduce increased perioperative BNP or IL-6 in CABG surgical patients, decreases the incidence of postoperative morbidity.

Acknowledgements

Conflicts of interest

None declared.

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