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The Potential Predictive Value of Preoperative Brain Natriuretic Peptide Levels in Coronary Artery Bypass Grafting Surgery

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Abstract: *Aims*: The aim of this study was to assess whether preoperative and postoperative brain natriuretic peptide (BNP) levels could be used as predictors of postoperative complications and outcome in patients with coronary artery disease and ischemic heart failure undergoing on-pump or off-pump coronary artery bypass grafting surgery (CABG).

Methods and Results: Fifty-eight patients (56 males and two females) with a median age of 65.3±9.9 years were included in the study. Thirty-eight patients (65.5%) underwent on-pump CABG, and 20 patients (34.5%) underwent off-pump CABG. BNP levels were determined within 24 hours before CABG and serially at 6 hours, 24 hours, 3, 7 and 30 days after CABG. Creatine phosphokinase myocardial band (CK-MB) levels were measured 1, 3, and 7 days after CABG. BNP and CK-MB levels did not differ significantly between the two groups at any time point. Preoperative BNP levels independently predicted the occurrence of cardiogenic shock and more importantly, short-term mortality. Neither preoperative left ventricular ejection fraction nor postoperative BNP or CK-MB levels at any time point showed any significant independent prognostic value for any postoperative complication. *Conclusion*: Our results suggest that it may be prudent to more closely monitor patients with higher preoperative BNP levels for possible postoperative complications.

Keywords: Brain natriuretic peptide, coronary artery bypass grafting surgery, coronary artery disease, ischemic heart failure, prognosis, off-pump coronary artery bypass grafting surgery.

INTRODUCTION

Coronary artery bypass grafting surgery (CABG) is one of the most effective therapies for coronary artery disease (CAD). CABG is conventionally performed with the use of cardiopulmonary bypass (CPB). Nevertheless, CPB has been associated with an increased frequency of complications [1-6]. CABG without using extra-corporeal circulation eliminates CPB to accomplish CABG and recent randomized studies comparing on- and off-pump procedures showed comparable cardiac outcome [7-11] and decreased morbidity and mortality in off-pump CABG patients [6-13].

However, morbidity associated with CABG is still a matter of concern. A variety of risk factors have been described to help delineate risk assessment of patients undergoing CABG, including preoperative left ventricular ejection fraction (LVEF)[14,15] and postoperative increase in creatine phosphokinase myocardial band (CK-MB) levels [16-22]. However, no gold standard to effectively predict postoperative complications currently exists [23]. A valuable addition to the preoperative evaluation would be a quantitative, cost-effective, time-efficient serum marker capable of accurately predicting postoperative morbidity and mortality.

Brain natriuretic peptide (BNP) is a 32-amino acid peptide primarily synthesized in the cardiac ventricle and is being released in response to ventricular dilatation and pressure overload [24,25]. Since BNP accurately identifies LV dysfunction [26-29], BNP measurement might be useful in risk stratification of patients undergoing CABG. However, there is a paucity of data regarding the predictive value of BNP in this setting, especially in off-pump CABG [15,23,30-35].

The aim of this study was to determine the secretion pattern of BNP in patients with CAD and ischemic heart failure undergoing on-pump or off-pump CABG and to assess whether preoperative and postoperative BNP levels could be used as predictors of postoperative complications and outcome.

PATIENTS AND METHODOLOGY

This prospective study included consecutive patients with angiographically verified CAD referred for elective CABG. In addition, all patients had LV systolic impairment measured by ventriculography or echocardiographic examination.

At baseline, demographic data (age, sex), history of conventional vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking habit, alcohol abuse), and of atrial fibrillation, chronic obstructive pulmonary disease (COPD) and chronic kidney disease were obtained. Hyperlipidemia was defined as low-density lipoprotein cholesterol (LDL-C) > 100 mg/dl or treatment with lipid-lowering medi-

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1876-5335/08

cation. Chronic kidney disease was defined as creatinine clearance < 60 ml/min/1.73m^2 [36].

We determined heart rate, systolic and diastolic arterial blood pressure, and heart failure status according to New York Heart Association (NYHA). Routine laboratory investigations were performed the first day after admission to the hospital after overnight fasting, and included levels of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, urea, creatinine, uric acid, fibrinogen, hemoglobin, and hematocrit. All laboratory tests were performed on a Roche/Hitachi 912 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). LDL-C was calculated using Friedewald's formula [37]. Preoperative renal function was assessed by baseline creatinine clearance, calculated by the Modification of Diet in Renal Disease equation [36]. CK-MB was measured 1, 3, and 7 days after surgery using a Roche/Hitachi 912 analyzer (Roche Diagnostics GmbH, Mannheim, Germany)(normal range < 24 IU/l).

Blood samples for BNP measurement were obtained within 24 hours before surgery and serially at 6 hours, 24 hours, 3, 7 and 30 days after the operation. Blood samples for BNP were taken into EDTA tubes in which 250 µl of aprotinin had been added to inhibit breakdown of the hormone. All samples were centrifuged immediately after collection at 2000 turns for 20 min and were stored at -80℃ until analyzed. BNP concentration was determined by a competitive enzyme-linked immunosorbent assay (ELISA) in 96-well microtiter plates (micro-ELISA) [38,39]. All reagents and materials were supplied by Peninsula Laboratories Inc., CA, USA. The minimum detectable BNP concentration of the assay is 0.06 ng/mL and the intra-assay and inter-assay coefficient of variation were 5% and 14% respectively.

All patients were submitted preoperatively to comprehensive echocardiography (EnVisor C Ultrasound System, Philips Medical Systems, Eindhoven, Netherlands). Measurements included interventricular septal thickness (IVS), posterior wall thickness (PW), LV diameter at end-diastole (LVDd), and right ventricular diameter at end-diastole. LVEF was calculated according to the Teichholz equations [40]. Echocardiography was repeated when clinically indicated and in all patients on the 7th day post-CABG and at a follow-up visit on the 30th day post-operatively.

Left-heart catheterization was performed preoperatively in all patients. We measured LVEF, systemic and pulmonary vascular resistance, central venous pressure, pulmonary capillary wedge pressure, pulmonary arterial systolic pressure, left and right ventricular stroke work index, stroke volume and stroke volume index. Cardiac output was measured by the thermodilution method, and cardiac index was calculated.

The same surgeon operated on all patients. On-pump CABG was carried out with normothermic (37ºC) CPB using intermittent antegrade hyperkalaemic warm blood cardioplegia supplemented with magnesium [41]. During off-pump procedures, a stabilizer (Koros Surgical Instruments, Moorpark, CA, USA) was used to expose and stabilize the target coronary artery. The left internal thoracic artery was anastomosed to the left anterior descending artery, and the right internal thoracic artery, radial artery and/or saphenous vein graft were used for other lesions [42].

Both intraoperatively and postoperatively – until exit from the hospital – we monitored and recorded the occurrence of myocardial infarction, cardiac enzyme elevation, malignant arrhythmias, emergency reintubation, hemodynamic instability requiring inotropic support, cardiogenic shock, requirement for intraaortic balloon counterpulsation, acute respiratory failure, acute renal failure requiring dialysis, and pleural infusion. We also recorded duration of ventilator dependence, intensive care unit (ICU) length of stay, and total hospital length of stay, as well as readmission within 30 days for cardiac reasons, and mortality and cause of death within 30 days postoperatively. Diagnosis of myocardial infarction was based on 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 CK-MB levels ten times over the upper limit of normal range.

All patients gave written informed consent before study entry. The study was conducted in accordance with the Declaration of Helsinki.

All data were analyzed using the statistical package SPSS (version 10.0; SPSS Inc., Chicago, IL). Continuous data are presented as mean±SD and categorical data as absolute numbers and percentages. Because BNP values were not normally distributed, they were logarithmically transformed for statistical analysis, but are presented in the study as non-transformed median and range. Correlations between variables were assessed using Pearson's correlation. The Student's t-test and chi-square test were used for comparisons of continuous and categorical variables between groups respectively. The significance of changes in LVEF and BNP before and after operation was evaluated with analysis of variance (ANOVA) for repeated measures. In addition, the variation over time of BNP was analyzed according to the type of CABG using analysis of covariance (ANCOVA). The predictive value of BNP concentrations and other relevant variables for intra- and post-operative complications was assessed by use of logistic regression, including all variables that predicted complications in univariate analysis. Odds ratios (OR) were generated and expressed with 95% confidence intervals (CI). The utility of BNP as a prognostic indicator of intraoperative and postoperative complications was also evaluated using receiver operating characteristic (ROC) curves. In all cases, a 2-tailed p value less than 0.05 was considered statistically significant.

RESULTS

Fifty-eight patients (56 males and two females) with a median age of 65.3±9.9 years were included in the study. Thirty-eight patients (65.5%) underwent on-pump CABG, and 20 patients (34.5%) underwent off-pump CABG. Preoperative patient characteristics are presented in Tables **1** and **2**. Preoperatively, patients who underwent on-pump CABG were significantly younger (p=0.038), had lower systolic blood pressure (p=0.005), lower diastolic blood pressure (p=0.034), and higher uric acid levels (p=0.043). In addition, the former had a lower number of diseased vessels (p=0.005) and significantly greater cardiac output (p=0.007) compared with patients who underwent off-pump CABG.

Median preoperative BNP concentration was 1.0 ng/ml (range, 0.1-64.2 ng/ml). BNP correlated significantly with age (r=0.342, p=0.009), creatinine clearance (r=-0.303,

Table 1. Demographics, Vascular Risk Factors and Vascular Diseases of the Study Population

Parameter	On-Pump CABG (n=38)	Off-Pump CABG (n=20)	p*	Overall (n=58)
Age (years)	63.4±8.9	69.0±10.7	0.038	65.3±9.9
Males (%)	94.7	100.0	0.77	96.6
Hypertension (%)	65.8	80.0	0.41	70.7
Diabetes mellitus (%)	28.9	30.0	1.00	29.3
Atrial fibrillation (%)	13.2	10.0	1.00	12.1
Previous percutaneous transluminal coronary angioplasty (%)	2.6	10.0	0.56	5.2
Previous CABG (%)	10.5	10.0	1.00	10.3
Previous myocardial infarction (%)	86.8	70.0	0.23	81.0
Unstable angina (%)	44.7	40.0	0.95	43.1
Duration of angina (months)	0.9±0.8	2.5±3.8	0.09	1.6±2.5
Main vessel disease (%)	28.9	30.0	1.00	29.3
Number of diseased vessels	2.4±0.7	2.8±0.4	0.005	2.6±0.6
Chronic kidney disease (%)	31.6	30.0	1.00	31.0
Chronic heart failure				
NYHA functional class II (%)	71.1	80.0	0.67	74.1
NYHA functional class III (%)	28.9	20.0	0.67	25.9
Previous stroke (%)	10.5	10.0	1.00	10.3
Hyperlipidemia (%)	86.8	80.0	0.76	84.5
Smoking (%)	60.5	45.0	0.39	55.2
Alcohol abuse (%)	2.6	5.0	1.00	3.4

* For the comparison between patients who underwent on-pump and those who underwent off-pump CABG.

Table 2. Clinical and Laboratory Findings at Admission (Mean±SD)

Parameter	On-Pump CABG (n=38)	Off-Pump CABG (n=20)	p*	Overall (n=58)
Systolic BP (mmHg)	120.1±17.4	133.8±16.3	0.005	124.9±18.1
Diastolic BP (mmHg)	72.5±8.8	78.2±11.0	0.034	74.5±9.9
Pulse rate (beats/min)	73.2±9.1	73.4±8.3	0.94	73.2±8.7
Body mass index (kg/m^2)	28.3±4.2	27.2±2.9	0.34	27.9±3.9
Glucose (mg/dl)	123.0±46.6	127.4±43.0	0.72	124.5±45.1
Total cholesterol (mg/dl)	173.7±41.8	175.8±58.7	0.87	174.4±47.8
LDL cholesterol (mg/dl)	109.7±35.9	110.6±57.7	0.94	110.0±44.1
HDL cholesterol (mg/dl)	36.5±9.4	40.0±10.2	0.19	37.7±9.7
Triglycerides (mg/dl)	137.6±47.2	124.3±57.3	0.35	133.0±50.8
Urea (mg/dl)	48.0±25.5	36.9±10.1	0.07	44.1±21.9
Creatinine (mg/dl)	1.2±0.6	1.1±0.3	0.52	1.1±0.5
Creatinine clearance (ml/min/1.73 m^2)	75.1±24.0	77.3±23.6	0.74	75.9±23.7
Uric acid (mg/dl)	7.1±1.9	6.1±1.1	0.043	6.7±1.7
Fibrinogen (mg/dl)	398.0±76.4	376.7±88.3	0.38	389.4±81.1
BNP (median (range)) (ng/ml)	1.2 (0.1-64.2)	0.8 (0.1-7.1)	0.08	1.0 (0.1-64.2)

*For the comparison between patients who underwent on-pump and those who underwent off-pump CABG.

p=0.022), cardiac index (r=-0.281, p=0.048), and LVDd (r=0.283, p=0.033). In addition, preoperative BNP levels showed significant negative correlation with preoperative LVEF, as determined both by echocardiogram and during ventriculography (r=-0.392, p=0.003 and r=-0.451, p=0.004, respectively).

Complete revascularization was achieved in all patients. Two patients (3.4%) had a single coronary graft, 19 had two grafts (32.8%), 34 had three grafts (58.6%), and three had four grafts (5.2%). Intraoperative and postoperative complications are summarized in Tables **3** and **4** respectively. There were no significant differences in the rate of complications between patients undergoing on-pump or off-pump CABG. None of the patients suffered a required reoperation, and none required readmission within the follow-up period. There were four hospital deaths. In the on-pump CABG group, two patients died (5.3%), five and 68 days postoperatively respectively, because of septic shock and multiorganic failure respectively. In the off-pump CABG group, two patients died (10.0%), three and 16 days postoperatively respectively, because of ventricular fibrillation and septic shock respectively. Among the patients who left the hospital, none died within 30 days after surgery.

In both patients in the on-pump and off-pump CABG groups, BNP changed significantly postoperatively (p<0.0005 and p=0.025 respectively) (Fig. **1**). In the group undergoing on-pump CABG, BNP concentrations increased progressively and reached their peak on the third day after the operation to 2.51 ng/ml (range, 0.1-19.43 ng/ml, p=0.027 compared to preoperative levels), decreased gradually thereafter, but remained above baseline levels the thirtieth day after CABG (Fig. **1**). In contrast, in the group undergoing off-pump CABG, BNP concentrations decreased immediately after CABG, albeit not significantly, increased gradually thereafter, also reaching highest values the third day after the operation to 1.62 ng/ml (range, 0.1-8.22 ng/ml,

Table 3. Number of Patients who Experienced Intraoperative Complications

Parameter	On-Pump CABG (n=38)	Off-Pump CABG (n=20)	p*	Overall (n=58)
Arrhythmia	2	3	0.44	5
Intra-aortic balloon pump	1	3	0.22	4
Cardiogenic shock	0	1	0.74	1
Dopamine > 3 μg/kg/min (%)	2	1	1.00	3
Epinephrine (%)	13	11	0.21	24
Milrinone (%)	10	6	1.00	16

* For the comparison between patients who underwent on-pump and those who underwent off-pump CABG.

Table 4. Number of Patients who Experienced Postoperative Complications

Parameter	On-Pump CABG (n=38)	Off-Pump CABG (n=20)	p*	Overall (n=58)
Non-ST segment elevation myocardial infarction	1	0	1.00	1
Cardiac enzyme elevation	2	2	0.89	4
Cardiorespiratory arrest	1	1	1.00	2
Arrhythmia	11	5	0.99	16
Defibrillation	0	1	0.74	1
Inotropic support	33	16	0.76	49
Intra-aortic balloon pump	2	3	0.44	5
Cardiogenic shock	2	0	0.77	2
Pleural effusion	10	5	1.00	15
Reintubation	3	2	1.00	5
Acute respiratory failure	5	1	0.61	6
Acute renal failure	1	0	1.00	1
Ventilator dependence > 24 hours	3	2	1.00	5
Intensive care unit length of stay > 3 days	7	2	0.64	9
Total hospital length of stay > 9 days	9	4	1.00	13
Death	2	2	0.89	4

* For the comparison between patients who underwent on-pump and those who underwent off-pump CABG.

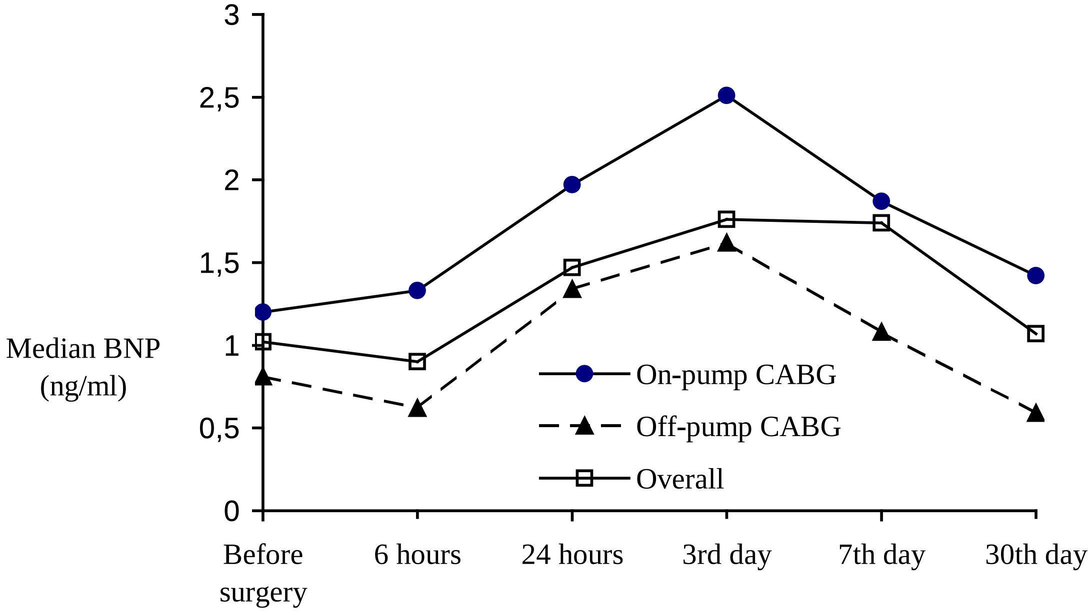

Fig. (1). Time courses of brain natriuretic peptide (BNP) concentration in patients undergoing on-pump CABG, off-pump CABG, and overall (median values).

p=0.032 compared to preoperative levels), and decreased progressively thereafter to levels lower than baseline levels the thirtieth day after CABG (Fig. **1**). In both groups, preoperative BNP levels and BNP levels at the thirtieth postoperative day did not differ significantly. In both groups, there was a very strong correlation between baseline BNP levels and BNP values at all time points. However, the differences in BNP levels between the two patient groups were not significant at any time point. Furthermore, the postoperative time course of BNP concentration was independent of the number of diseased vessels.

Duration of ventilation dependence and postoperative days spent in the ICU significantly correlated with preoperative BNP levels (r=0.339, p=0.01 and r=0.266, p=0.045 respectively). In univariate analysis, preoperative BNP concentration predicted the occurrence of four major postoperative complications: requirement of inotropic support, cardiogenic shock, reintubation, and death. Except preoperative BNP concentrations, LVDd was the only other parameter associated with a higher risk of postoperative requirement of inotropic support in univariate analysis. However, in multivariate analysis, only LVDd was found to be an independent predictor of postoperative requirement of inotropic support with an odds ratio of 24.15 (95% confidence interval, 2.04-286.47; p=0.012). Regarding cardiogenic shock, preoperative BNP concentration was the only independent predictor with an odds ratio of 26.83 (95% confidence interval, 1.22-590.97; p=0.037). Regarding reintubation, in univariate analysis, age, COPD, chronic kidney disease, and NYHA class III showed predictive value. Nevertheless, in multivariate analysis, none of these parameters was independently associated with reintubation. Finally, regarding mortality, in univariate analysis, presence of COPD was the only other parameter besides preoperative BNP concentration associated with a higher risk of death. In multivariate analysis, both these parameters were associated with mortality; preoperative BNP concentration with an odds ratio of 13.58 (95% confidence interval, 1.29-142.76; p=0.030) and COPD with an odds ratio of 53.94 (95% confidence interval, 2.27-1281.37; p=0.014). Preoperative BNP concentration could not predict other postoperative complications, neither any of the intraoperative complications. In addition, postoperative BNP concentrations could not predict any postoperative complication. In a separate analysis according to type of CABG, among patients who underwent on-pump CABG, preoperative BNP concentration was the only parameter that could predict mortality with an odds ratio of 30.08 (95% confidence interval, 1.01-898.87; p=0.050), whereas in the off-pump CABG group preoperative BNP levels had no predictive value, possibly due to the small number of patients in this group.

The ROC curves for BNP as a predictor of postoperative requirement of inotropic support, development of cardiogenic shock, requirement of reintubation, and mortality, had areas under the curve of 0.701, 0.900, 0.777 and 0.774 respectively. A preoperative BNP of 2.1 pg/ml had a sensitivity of 33%, 100%, 80%, and 75% and a specificity of 89%, 73%, 75%, and 74% for predicting the postoperative requirement of inotropic support, development of cardiogenic shock, reintubation, and mortality respectively.

Compared with pre-CABG assessment, LVEF increased significantly as early as 7 days postoperatively (41.8±8.5%, p<0.0005 compared to preoperative levels) and even more at 30 days post-CABG (47.9±9.1%, p<0.0005 compared to preoperative levels and p=0.005 compared to LVEF levels at 7^{th} day) (Fig. **2**). Patients who underwent off-pump CABG showed greater increases in LVEF at the 30^{th} postoperative day compared to the ones who underwent on-pump CABG (53.2±7.8% *vs* 45.5±8.7%, p<0.0005). Neither preoperative nor postoperative BNP levels could identify the patients that showed improvement in LVEF. Finally, lower preoperative LVEF, as determined by echocardiography, predicted the need for prolonged stay in the ICU postoperatively in univariate analysis, and so did previous CABG, previous stroke,

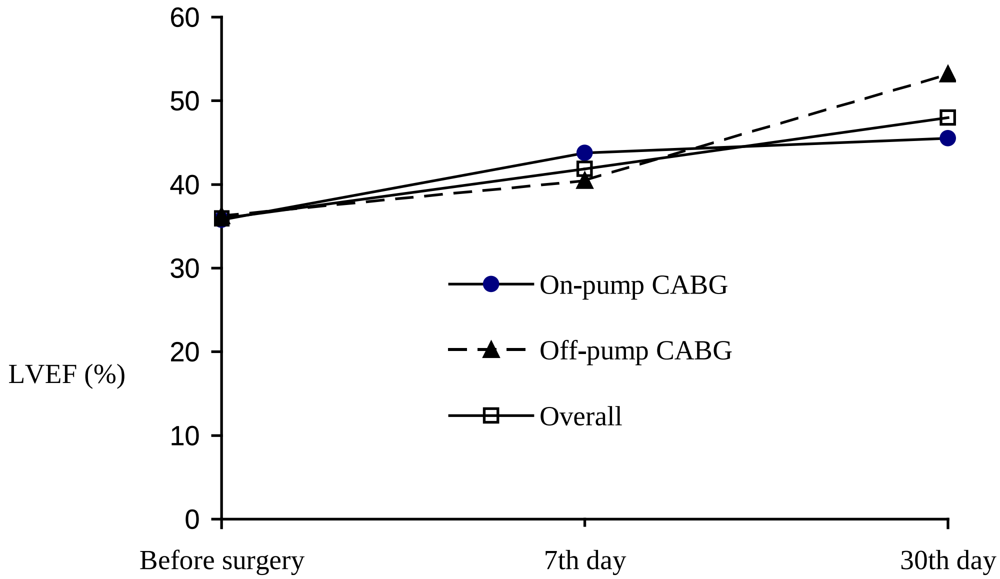

Fig. (2). Time courses of left ventricular ejection fraction (LVEF) in patients undergoing on-pump CABG, off-pump CABG, and overall (mean±SD).

presence of atrial fibrillation preoperatively, and lower creatinine clearance. However, in multivariate analysis, none of these parameters could independently predict the occurrence of this complication.

The postoperative secretion pattern of CK-MB was independent of the type of CABG (Fig. **3**). Furthermore, CK-MB values did not correlate with identically timed BNP concentrations and more importantly, did not show significant independent prognostic value for any postoperative complication.

DISCUSSION

The main finding of this study is that, in patients with CAD and ischemic heart failure undergoing CABG, preoperative BNP levels independently predict the occurrence of cardiogenic shock and more importantly, short-term mortality.

The principal physiological effects of BNP include natriuresis, vasodilatation, and inhibition of renin-angiotensin-aldosterone system and sympathetic outflow [24,25]. Several recent studies have demonstrated that BNP is a reliable index of LV dysfunction [26-29], and thus BNP has emerged as a key biomarker for the diagnosis, evaluation and management of congestive heart failure [43]. In the present study, plasma BNP showed significant negative correlation with preoperative EF, as determined both by echocardiogram and during ventriculography, and with cardiac index, which is consistent with the data reported by other investigators [26-29]. Therefore, it seems logical that preoperative BNP could be capable

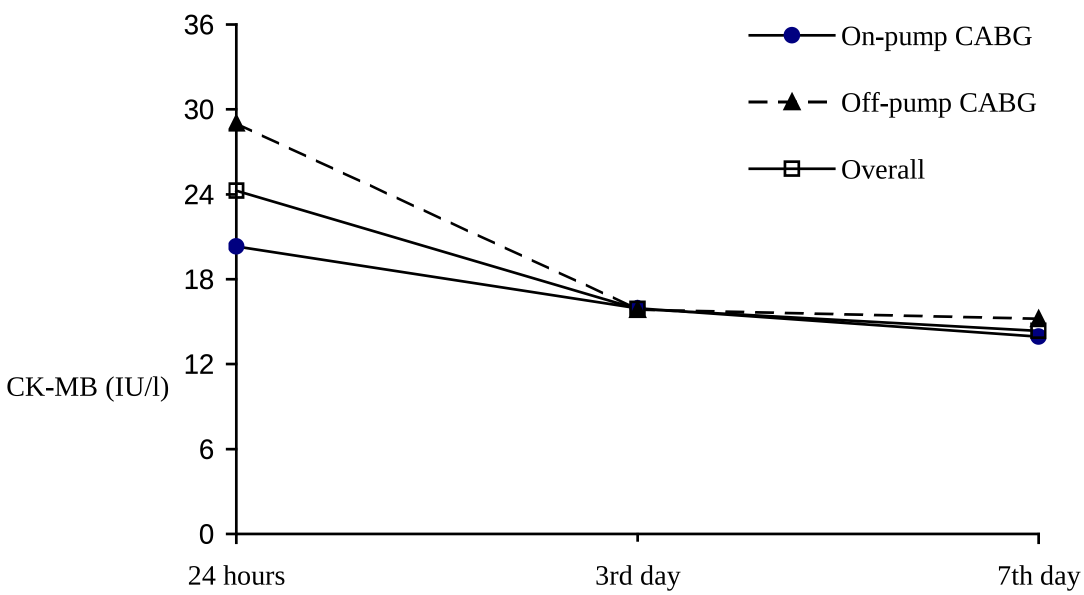

Fig. (3). Secretion patterns of creatine phosphokinase myocardial band (CK-MB) in patients undergoing on-pump CABG, off-pump CABG, and overall (mean±SD).

of predicting postoperative outcomes.

Our data confirm the predictive power of BNP and its potential prognostic role. Increased preoperative BNP concentrations predicted postoperative morbidity and mortality, in agreement with previous reports [23,30-35]. Cardiac dysfunction is a frequent complication of CABG, results from cardioplegia and CPB, as well as from ongoing ischaemia, and worsens the patients' prognosis [44]. Our results demonstrate that a lot of patients undergoing CABG develop LV dysfunction, manifesting either as hemodynamic instability requiring inotropic support or, less frequently, as cardiogenic shock. Risk stratification is therefore an important issue in these patients. A limited number of reports suggest that the occurrence of acute heart failure after cardiac surgery can be predicted by the preoperative BNP concentration [30,31], and this was evident in this study as well. But even more importantly, preoperative BNP concentrations predicted increased mortality during short-term follow-up, providing additional evidence to the available scant data [23,32]. The odds ratio in our study are characterized by rather wide confidence intervals; the low rate of complications and the relatively small number of patients are the most likely explanations for this finding, but does not necessarily compromise the predictive significance of preoperative BNP levels. Finally, since postoperative BNP concentration reflects perioperative cardiac injury [15,45], in certain studies postoperative BNP concentration was better predictor for the occurrence of post-CABG complications than preoperative BNP concentration [15,23,33], although other authors have reported opposite findings [32,34]. However, postoperative BNP levels did not carry significant predictive value in our study.

Low LVEF alone has been reported to represent one of the best independent predictors of postoperative morbidity and mortality [14,15]. However, other authors have shown that preoperative LVEF does not have significant predictive value [23]. In our study group as well, LVEF, although showing significant correlation with preoperative BNP levels, could not predict any postoperative complications, in striking contrast with BNP. In addition, preoperative functional status reflected by NYHA class did not have any predictive value as well.

The usefulness of CK-MB as a reliable marker of perioperative myocardial ischaemia and injury after CABG, both on-pump and off-pump, has been demonstrated [46,47]. There is growing evidence that even small elevations of CK-MB in the periprocedural period are independently associated with a significant increase in myocardial infarction, postoperative LV dysfunction and both early and late mortality [16-22]. One might speculate that the combination of a necrosis marker – such as CK-MB – and a volume and pressure marker – such as BNP – might be useful for further risk stratification of patients before and in the early postoperative state. However, this was not apparent in our study and postoperative CK-MB concentrations did not exhibit significant predictive value. Thus, our data do not support routine use of CK-MB measurement following CABG to further delineate short-term risk of complications.

In the present study, we have also evaluated the behaviour of BNP levels secondary to CABG. In agreement with several previous reports [15,31-33,44,48-50], we observed a marked and systematic postoperative increase of BNP levels, reaching a peak 3 days post-CABG. It has also been reported that BNP release is enhanced not only in the early phase after CABG but also after as late as one week postoperatively [31,49], and this was observed in our study as well. Moreover, increased BNP levels tended to return to the baseline values as early as 30 days from cardiac surgery, in accordance to previous reports [31]. Other studies however, have showed more delayed reductions in BNP levels after revascularization, from 3 to 10 months of follow up [49,51]. Lack of more early determinations of BNP concentration and differences in the study population might account for these discrepant results. Regarding the effect of CPB on the time course of BNP concentration, there is a paucity of relevant data [34,35,50,52]. In two recent studies in patients undergoing off-pump CABG, BNP concentrations peaked 48 h after surgery and began to decrease at 72 h, similarly to our findings [34,35]. In our comparative study, in accordance to a previous one [50], postoperative BNP levels did not differ significantly between patients undergoing on-pump or off-pump CABG. The elevation of BNP level lasted longer in the on-pump CABG group, however this difference was not significant.

The pathophysiology of increased production of BNP post-CABG is unclear. It may result from acute left ventricular dysfunction and also relate to increased preload on the heart resulting from increased intravascular volume or transient diastolic dysfunction [15,32,50]. In addition, it is well established that ischemic insult constitutes an independent stimulus for BNP release even in the absence of LV dysfunction [32,53-56]. It has thus been suggested that BNP stimulation in CABG patients may be due to the augmented regional wall stretch induced by perioperative myocardial ischemia [2,32]. It has also been demonstrated that patients with significant myocardial damage have higher BNP levels [15]. However, in certain studies, including ours, BNP concentrations did not correlate with CK-MB levels, suggesting that the degree of myocardial necrosis post-CABG is insufficient to affect ventricular function and circulating BNP concentrations [33,50]. In addition, and in contrast to previous reports [49,57], patients with more extensive CAD did not exhibit higher BNP levels postoperatively. Finally, it must be emphasized that BNP release, except from constituting a marker of vascular and myocyte injury, also represents a counter-regulatory system for protection of cardiac muscle [25]. Thus, postoperative increase of BNP might not reflect a state of acute perioperative heart failure or myocardial damage [48]. The lack of predictive value of postoperative BNP levels regarding the occurrence of complications further supports this assumption.

It is well established that CPB, presumably because of the blood's contact with foreign materials and its exposure to abnormal shear forces [58], causes an increase of circulating cathecholamines and endothelin, augments oxidative stress, activates the coagulation, fibrinolytic, kallikrein, and complement cascades and may enhance the postoperative inflammatory response [1-5]. Furthermore, cardiac operations with CPB result in heart ischemia during the period of heart arrest, while heart reperfusion after this ischemic period produces myocardial damage and eventual necrosis [59]. Finally, CPB produces numerous other important causes of myocardial damage, including atriotomy, poor myocardial protection, and myocardial stunning [15,59]. In contrast, CABG without using extra-corporeal circulation is associated with reduced cytokine responses, decreased oxidative stress, and less ischemic and reperfusion myocardial injury [3-6,50,59-61]. Indeed, a number of studies have shown that patients operated with CPB had more circulating CK-MB postoperatively than patients operated off-pump, suggesting a reduced myocardial cell damage with off-pump CABG [7,10,11,47,50,59,62-64]. More importantly, recent randomized studies comparing the two techniques, showed comparable cardiac outcome [7-11] and reduced perioperative myocardial infarction, reduced postoperative bleeding, preservation of renal function, lower surgical reexploration rates, shortened hospital stays, economical advantages, and decreased operative mortality [7-13,65]. In this relatively small study, we could not identify significant differences in CK-MB release or, more importantly, in the occurrence of complications between patients undergoing on-pump or off-pump CABG. However, it must be noted that patients in the on-pump group had more favourable preoperative characteristics and this might have contributed to this lack of differences between groups.

CABG is being performed with increasing frequency in patients with severe LV dysfunction with favorable results [66,67]. This is based on the finding that in many patients with CAD, impairment of LV function is not always irreversible, since it results from the presence of viable, hibernating myocardium, rather than of irreversible fibrosis [68]. The important characteristic of hibernating myocardium is its ability to improve its contractile function after myocardial revascularization [69]. The results of this study are in agreement with the above-cited reports [66,67], and show that patients with compromised LV function have significant improvement of LVEF, as well as good in-hospital outcomes and medium-term survival. In this study of patients with CAD and LV dysfunction, plasma BNP concentrations were increased in proportion to the degree of hemodynamic impairment, whereas a decrement was observed after coronary revascularization, which paralleled the significant improvement of LV function. It has previously been demonstrated that preoperative plasma levels of BNP could predict the post-CABG recovery of the LV function [51]; however, in this study neither preoperative nor postoperative BNP levels could predict this favorable outcome.

Our study has several limitations. We studied only 58 patients and among them only 2 were women. Therefore, the statistical power to identify predictors for adverse early outcomes was insufficient. This might explain why neither LVEF nor CK-MB levels predicted outcome in our study, in contrast to previous larger studies. We chose this approach because the existing data on the predictive value of preoperative BNP levels in patients undergoing CABG are limited. We therefore conducted this pilot study to gain more insight on the topic. Another limitation is that patients were not randomly allocated to on-pump or off-pump CABG. This is an important bias which could affect the results. Finally, the mortality rates in our cohort were quite high and this might reflect the characteristics of our study population (i.e. patients with CAD and ischemic heart failure). Therefore, our findings might not apply to all patients undergoing CABG.

CONCLUSION

Preoperative BNP levels have considerable predictive value in patients with CAD and ischemic heart failure undergoing CABG. Our results also suggest that it may be prudent to more closely monitor patients with higher preoperative BNP levels for possible postoperative complications. Further studies on larger and more diverse populations are warranted to compare predictive ability of preoperative BNP to currently applied factors and to evaluate potential for integration of this marker into preoperative evaluation. Preoperative BNP will probably need to be assessed in combination with other predictive factors (e.g. LVEF, CK-MB or troponin I) to improve risk stratification in patients undergoing CABG.

ABBREVIATIONS

BNP	=	Brain natriuretic peptide
CABG	=	Coronary artery bypass grafting surgery
CK-MB	=	Creatine phosphokinase myocardial band
CAD	=	Coronary artery disease
CPB	=	Cardiopulmonary bypass
LVEF	=	Left ventricular ejection fraction
COPD	=	Chronic obstructive pulmonary disease
LDL-C	=	Low-density lipoprotein cholesterol
NYHA	=	New York Heart Association
HDL-C	=	High-density lipoprotein cholesterol
ELISA	=	Enzyme-linked immunosorbent assay
IVS	=	Interventricular septal thickness
PW	=	Posterior wall thickness
LVDd	=	LV diameter at end-diastole
ICU	=	Intensive care unit
ANOVA	=	Analysis of variance
ANCOVA	=	Analysis of covariance
OR	=	Odds ratios
CI	=	Confidence intervals
ROC	=	Receiver operating characteristic

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Received: November 13, 2008 Revised: November 24, 2008 Accepted: November 25, 2008