J. Exp. Biomed. Sci. 2010, 16(4): 247~258

Preoperative Levels of Hematological and Biochemical Indices Affect Perioperative Variables in Adult Patients with Coronary Artery Bypass Graft Surgery

Seok-Cheol Choi[1], Byungkyu Cho[2], Yong Hwan Lee[2] and Kyung-Soo Chang[1,†]

[1]Department of Clinical Laboratory Science, College of Health Sciences, Catholic University of Pusan, Busan 609-757, Korea,
[2]Department of Preventive Medicine, Kosin University, College of Medicine, Busan 602-702, Korea

The objective of this research was to evaluate the relationships of preoperative (Pre-OP) levels of hematological and biochemical indices to perioperative variables in patients that underwent coronary artery bypass graft surgery (CABG). Pre-OP levels of hematological factors [total white blood cells (T-WBC), erythrocytes, hemoglobin, hematocrit, glycohemoglobin A1c (HbA1c), or platelet] were negatively or positively related with biochemical indices [alanine aminotransferase (ALT), bilirubin, glucose, fructosamine, triglyceride, and high density lipoprotein cholesterol (HDL)]. Pre-OP levels of hematological factors and biochemical indices were negatively or positively correlated with echocardiographic variables. Pre-OP level of HbA1c had a relationship with C-reactive protein. Pre-OP levels of aspartate aminotransferase (AST), ALT, HDL, glucose, fructosamine, or blood urea nitrogen (BUN) were positively or negatively associated with Pre-OP levels of cardiac markers (brain natriuretic peptide, troponin-I, creatine kinase isoenzyme 2, or CRP). Pre-OP levels of hematological factors (excepting T-WBC) related with operation time (OPT), postoperative mechanical ventilation time (POMVT), intensive care unit-period (ICU-period) or hospitalization. Pre-OP levels of AST, ALT, bilirubin, triglyceride, HDL, low dwensity lipoprotein, fructosamine, or BUN were positively or negatively correlated with OPT, graft numbers, POMVT, ICU-period or hospitalization. Retrospective this study reveals that Pre-OP levels of hematological and biochemical markers are associated with echocardiographic variables, several cardiac markers and postoperative outcomes, suggesting that Pre-OP levels of hematological and biochemical markers may be useful predictors for the diagnosis and prognosis of coronary artery disease.

Key Words: CABG, Hematological factor, Biochemical indices, Echocardiography, Cardiac marker, Postoperative outcomes

INTRODUCTION

Clinical physicians have worried and studied for rapid and accurate diagnosis of coronary artery disease (CAD) and prediction of postoperative outcomes of coronary artery bypass graft surgery (CABG). Biochemical markers such as creatine kinase isoenzyme 2 (CK-MB), cardiac troponin-T or -I (cTnT or cTnI, respectively), and C-reactive protein (CRP) and electrocardiogram (EKG) have been confided in diagnosing and predicting coronary heart diseases. However, Sensitivity and specificity of CK-MB are <100% despite its usefulness for the diagnosis of acute myocardial infarction (AMI). The laboratory tests most utilized for the diagnosis of AMI are creatine kinase (CK, EC 2.7.3.2) and its MB isoenzyme (CK-MB) (Lee et al., 1986). Although measurement of CK-MB has been suggested to be the 'gold standard' for the diagnosis of myocardial infarction (MI), non-cardiac disorders may also cause increases of CK-MB (Medeiros et al., 1987). Changes on the EKG are the most important tool that should be utilized quickly after

*Received: 4 October, 2010 / Revised: 24 December, 2010
Accepted: 27 December, 2010
†Corresponding author: Kyung-Soo Chang, Department of Clinical Laboratory Science, College of Health Sciences, Catholic University of Pusan, Busan 609-757, Korea.
Tel: +82-51-510-0565, Fax: +82-51-510-0568
e-mail: kschang@cup.ac.kr

presentation of the suspected MI patient. However, the EKG is not a perfect instrument because its diagnostic sensitivity may be as low as 50% (Lee et al., 1987). The troponin complex consists of three subunits referred to as TnT, TnI and TnC. Myocardium contains TnT and TnI isoforms which are not present in skeletal muscles. Even though clinical laboratories are able to determine cTnT reliably as classical cardiac marker, an increase of cTnT levels have been documented in patients with end-stage renal disease (Katus et al., 1991). cTnI have been demonstrated as an excellent marker for the diagnosis of MI. In recent, clinical physicians have noted brain natriuretic peptide (BNP), which increases in patients with congestive heart failure, especially in those with severe hemodynamic impairment (Levin et al., 1998), and is a strong predictor of prognosis in patients with previous MI (Hall et al., 1994) and congestive heart failure (Dickstein et al., 1997).

Nevertheless, analysis of such cardiac markers must be offered a long time and expensive cost. In the United States, 23 million adults with no history of cardiovascular disease are classified as intermediate-risk by the Framingham score, meaning they have a 10-year risk for major CAD events of 10% to 20% (Ford et al., 2004). Patients with coronary syndromes, including coronary stenosis, spasm and MI are dramatically increasing in Korea. Therefore, rapid, reliable and cheap markers are very important for predicting perioperative outcomes as well as the diagnosis and prognosis of CAD.

Some evidences suggest a possibility that changes in biochemical indices appear to be responsible for the development of CAD (Schindhelm, 2009). In addition, hematological factors, which reflect normal and abnormal circulation in the cardiovascular system, may be associated with the development and prognosis of CAD.

This study was retrospectively designed and data were postoperatively reviewed to investigate whether preoperative levels of hematological and biochemical indices have any relationships with cardiac markers levels and perioperative outcomes in eighty-five adult patients that underwent coronary artery bypass grafting surgery (CABG).

MATERIALS AND METHODS

Study population

Data of eighty-five adult patients that underwent coronary artery bypass grafting surgery (CABG) were postoperatively reviewed in 'D' hospital. Blood or other samples were never collected from the patients and additional test were not performed for the present study. All patients were discharged from the hospital. We only evaluated the recorded-data for this study.

Methods

Analysis of variables. The following variables were preoperatively or postoperatively analyzed and recorded.

Echocardiography. On the recommendation of the American Society of Echocardiography, M-mode and two-dimensional method were applied for the all patients' echocardiograms.

Hematological factors. 2 mL of the blood was infused EDTA-containing CBC bottle for measuring hematological factors and they were determined by Sysmex XE-2100 (Sysmex Co., Japan).

Biochemical indices. 3 mL of the blood was separated into serum for analysis of biochemical markers. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) (liver markers), blood urea nitrogen (BUN), creatinine (renal markers), total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglyceride (lipid metabolism), glucose and fructosamine levels were measured by Autohumalyzer 9500 (Human Lab., Germany).

Cardiac markers. 3~5 mL of blood was injected into EDTA-bottle and plasma brain natriuretic peptide (BNP) concentrations were measured by fluorescence immunoassay with BNP kit (Triage®, Biosite, San Diego, USA). Detection ranges of BNP kit are 5~5,000 pg/ml and its reference value is <100 pg/mL. Preoperative levels of plasma C-reactive

protein (CRP) were measured by HITACHI 7600-210 instrument (Hitachi, Japan) with commercial CRP kit (Denka Co., Japan) (reference value; 0~0.5 mg/dl). Preoperative levels of plasma cTnI were determined by Access immunoassay system (Sanofi Diagnostic Pasteur, Inc., France) with commercial cTnI kit (Boehringer Mannheim, Germanny) (reference value <0.05 ng/ml). Preoperative levels of plasma CK-MB were analyzed by Toshba instrument (Toshba Co., Japan) with CK-MB kit (Wako Co., Japan) (reference value; 0~15 U/L).

Operative procedures. All patients received general anesthesia. After median sternotomy, left internal mammary artery, left radial artery, and great saphenous vein were harvested from all patients for CABG. 80~100 mg of heparin was intravenously injected and the heart was exposed. Cardiac apex was lifted for fixing appointed sites of anastomoses using cardiac holding apparatus (Octopus, Medtronic Inc., USA), and one to six vessels were anastomosed by one operator. After the anastomoses, blood flow was reestablished [assessment by HT 107 medical volume flowmeter (Transonic systems Inc., USA) (normal flow; >20 ml/min)] and 0.8~1.0-fold protamine of used heparin was administered.

Perioperative variables. Operation time (OPT), vessel grafting-numbers (graft-no.), postoperative mechanical ventilation-time (PMVT), ICU-staying periods (ICU-period) and hospitalized-day were recorded.

Table 1. Characteristics in study population

Parameter	Value
Sample size (no.)	85
Gender (M : F)	59:26
Age (year)	62.25±9.64
Height (cm)	164.25±8.08
Weight (kg)	67.03±11.71
BSA (m^2)	1.74±0.26
OP-time (min)	281.49±45.20
POMV-time (hr)	16.04±15.98
ICU-period (hr)	64.14±28.38
Hospitalization (day)	15.77±4.66
Graft-number (no.)	3.21±0.95

Data were expressed the mean ± SD (standard deviation).
Abbreviation: BSA, body surface area; OP, operation; POMV, postoperative mechanical ventilation; ICU, intensive care unit; Graft-number, number of vessel for coronary artery bypass graft surgery (CABG).

Statistical analysis

Data were presented as mean ± SD (standard deviation). Pearson's correlation-analysis was applied for the determination of association between preoperative levels of hematological or biochemical indices with cardiac markers (BNP, cTnI, CK-MB and CRP), echocardiographic parameter and perioperative variables (SAS program). Statistical significance was accepted with $P \leq 0.05$.

RESULTS AND DISCUSSION

Characteristics in study population

Table 1 shows clinical characteristics in study population. All patients had undergone CABG.

Preoperative echocardiography

The preoperative (Pre-OP) echocardiographic findings

Table 2. Preoperative results of echocardiographic parameters

Parameter	Value	Normal range
LVIDD (mm)	53.10±7.85	42~54
LVIDS (mm)	37.60±8.67*	24~26
PWD (mm)	9.15±1.52	8~11
LA dimension (mm)	41.23±6.07	27~44
LA volume (ml)	62.30±21.01*	<60
RVIDD (mm)	20.11±5.40	9~26
LVEF (%)	48.98±13.64*	55~76
SLMCA (%)	74.20±20.55*	0
SLAD (%)	88.27±13.30*	0
SLCX (%)	89.07±12.47*	0
SRCA (%)	93.51±11.20*	0
SBP (mmHg)	127.21±21.38	90~130
DBP (mmHg)	78.30±12.25	60~90

Data were expressed the mean ± SD.
*, abnormal value compared with the normal range.
Abbreviation: LVIDD, left ventricular internal dimension at diastole; LVIDS, left ventricular internal dimension at systole; PWD, posterior wall dimension; LA, left atrium; RVIDD, right ventricular internal dimension at diastole; LVEF, left ventricular ejection fraction; SLMCA, stenosis of left main coronary artery; SLAD, stenosis of left descending artery; SLCX, stenosis of left circumflex artery; SRCA, stenosis of right coronary artery; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Preoperative levels of hematological factors

Factor \ Time	Pre-OP	Normal range
T-WBC ($\times 10^3/\mu L$)	7.85±3.28	3.0~10
Erythrocyte ($\times 10^6/\mu L$)	4.18±0.59	3.6~4.9
Hemoglobin (g/dL)	13.04±1.99	11~15
Hematocrit (%)	37.46±5.29	33~44
HbA1c (%)	6.92±1.59*	4.4~6.0
Platelet ($\times 10^6/\mu L$)	159.10±106.02	140~360

Data were expressed as mean ± SD.
*, $P<0.05$ (compared with Pre-OP levels).
Abbreviations: T-WBC, total white blood cell; HbA1c, glycohemoglobin A1c.

Table 4. Preoperative levels of biochemical indices

Marker \ Time	Pre-OP	Normal range
AST (IU/L)	39.74±36.75*	10~35
ALT (IU/L)	38.61±34.26*	0~35
Bilirubin (mg/dL)	0.80±0.31	0.2~1.2
Glucose (mg/dL)	156.69±76.34*	76~110
Fructosamine (μmol/L)	272.57±55.18	205~285
Triglyceride (mg/dL)	159.10±106.02	30~200
T-cholesterol (mg/dL)	194.28±47.52	130~250
HDL (mg/dL)	36.09±11.93*	45~74
LDL (mg/dL)	113.34±39.40	65~140
BUN (mg/dL)	19.62±8.81	8~26
Creatinine (mg/dL)	1.07±0.33	0.6~1.2

Data were expressed as mean ± SD.
*, abnormal levels.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; T, total; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BUN, blood urea nitrogen.

are condensed in Table 2. Left ventricular internal dimension at systole (LVIDS) and left atrium (LA) volume were higher, whereas left ventricular ejection fraction (LVEF) was lower compared with each normal range, suggesting that coronary artery disease (CAD) can cause left ventricular dysfunction and hypertrophy and thereby lead to heart failure. The stenosis degree of coronary arteries was severe in most patients. The stenosis of coronary arteries results in a decline of oxygen and nutrients in the myocardium, contributing to myocardial injury and dysfunction attributable to anaerobic metabolism in the cell levels.

Pre-OP levels of hematological factors

Pre-OP levels of hematological factors are summarized in Table 3. The other factors, excepting glycohemoglobin Alc (HbAlc) were within normal ranges. HbAlc levels were greater than normal range. HbAlc is the predominant biomarker used in diabetes management. HbAlc could be used as a reliable indicator of glycemic control in the preceding 2~3 months. Nondiabetes people have a normal level under 6%, while uncontrolled diabetes patients can have levels exceeding 10% (True, 2009). And thus, the present data, which Pre-OP levels of HbAlc were about 7% represent that most patients that underwent CABG had a potential diabetes, leading to CAD.

Pre-OP levels of biochemical indices

Table 4 shows Pre-OP levels of biochemical indices. AST, ALT and glucose levels were higher, whereas HDL levels were lower than the normal range. However, increased ratios of AST and ALT levels were slight, whereas that of glucose levels was high. Fructosamine levels were close to the upper limit of normal range. Other indices were within normal ranges. Increased levels of AST, ALT (typical liver markers) and glucose may reflect that patients with CABG had a possibility of metabolic syndrome together with diabetes, which is responsible for the development of CAD (Schindhelm, 2009). Pre-OP high glucose and low HDL levels may contribute to the development of ischemic heart disease and CAD. Patients with diabetes have increased vascular vulnerability to atherogenic insults, leading to accelerated atherogenesis. During hyperglycemia, glycocalyx, a layer of proteoglycans coverting the endothelium, pertubation is mediated in vascular dysfunction and coagulation activation (Nieuwdorp et al., 2005), thereby resulting in the development of CAD. Hyperglycemia is associated with enhanced endothelial permeability, increased leukocyte-endothelium adhesion, and impaired nitric oxide (NO) bioavailability (Algenstaedt et al., 2003).

HDL plays a central role in many events involved in the development of atherosclerosis, and there is a negative correlation between plasma HDL levels and cardiovascular risk (Gordon et al., 1989). HDL presents several other antiatherogenic properties, such as inhibition of LDL aggregation and LDL non-enzymatic oxidation, which prevent cellular inflammatory events mediated by oxidized phos-

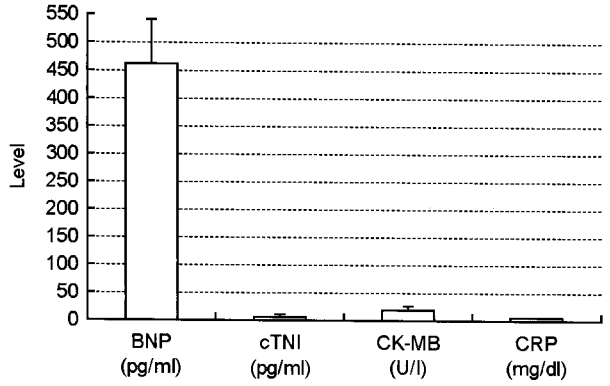

Fig. 1. Preoperative levels of blood cardiac markers in adult patients that underwent CABG surgery. Mean values of other cardiac markers, excepting CK-MB were significantly elevated compared with each normal range.

pholipids. Bancells et al. (2010) have demonstrated that HDL, at least in part through apo AI, inhibits phospholipase-C activity and electronegative LDL [LDL(−)] and monocyte-induced cytokine release, thereby counteracting the inflammatory effect of LDL(−). LDL(−) exerts inflammatory effects on endothelial cells, such as induction of cytokine release, cytotoxicity and apoptosis (Chen et al., 2003; Benitez et al., 2006). Therefore, the present data which show abnormally low HDL and normal LDL levels suggest that HDL levels are more important than LDL levels in the development of CAD.

Glucose molecules are joined to protein molecules to form stable ketoamines, or fructosamines, through glycation, a nonenzymatic mechanism involving a labile Schiff base intermediate and the Amadori rearrangement. The amount of fructosamine in serum is elevated in diabetes owing to abnormally high concentration of sugar in serum thus reflects the degree of glycemic control attained by the diabetic patient and is useful in monitoring the effectiveness of therapy in diabetes over a period of several weeks, in a manner analogous to the determination of HbAlc. The fructosamine level correlates best with average glucose levels in the previous 10~14 days (True, 2009). Unlikely HbAlc, which reflects the average blood sugar level over the past six to eight weeks, fructosamine represents the average blood sugar concentration over the two to three weeks. Thus a clinical advantage is that fructosamine responds more quickly to changes in therapy, thereby allowing for improved glycemic control. Diabetes is one of the classic risk factors for CAD. It is well known, in fact, that the risk for CAD is two to six fold higher in patients with type 2 diabetes than in patients without diabetes (Stamler et al., 1993). Even though the fructose levels in the present study were within normal range, many patients had diabetes. Therefore, the present data indicate that higher fructosamine levels may be a predictor for the CAD.

Pre-OP levels of cardiac markers

Fig. 1 displays Pre-OP levels of blood cardiac markers. Pre-OP levels of BNP, cTNI, CK-MB and CRP were 460.85±80.62 pg/mL, 3.12±0.65 pg/mL, 15.50±5.86 U/L, and 2.04±1.83 mg/dL, respectively. Although all cardiac markers were abnormally higher than the normal range, CK-MB levels were slightly higher compared with the normal range, suggesting that CK-MB may be a less powerful marker than the other cardiac markers for diagnosing CAD. BNP with a 32 aminoacid active hormone is secreted from the cardiac ventricles in response to volume expansion and pressure load (Steiner and Guqlin, 2008). BNP is a natriuretic, diuretic, and vasodilatory hormone. It offsets the effects of fluid overload, which causes stretch of the cardiac wall and triggers its secretion. Increases in BNP and pro-BNP levels are associated with heart failure and ischemic heart disease (IHD) (Singh et al., 2009). Furthermore, left ventricular end-diastolic wall stress and wall stiffness may be the predominant triggers of BNP secretion (Watanabe et al., 2006). Decreases in oxygen and energy supply attributable to stenosis or obstruction of coronary vessels can cause left ventricular wall stress and stiffness, resulting in the heart failure or dysfunction.

In the present study, higher BNP levels (the normal range; <60 pg/mL) in Pre-OP suggest that serum or plasma BNP can be considered to be a useful marker in diagnosing and prognosing CAD.

Association of hematological factors to biochemical indices

Table 5 shows association of Pre-OP levels of hematological factors to Pre-OP levels of biochemical indices. Pre-OP ALT levels had a negative relationship with Pre-OP levels of erythrocyte or hematocrit ($P<0.05$), suggesting

Table 5. Association of Pre-OP levels of hematological factors to Pre-OP levels of biochemical indices

Marker	T-WBC	Erythrocyte	Hemoglobin	Hematocrit	HbA1c	Platelet
AST (*r*)	ns	ns	ns	ns	ns	ns
ALT (*r*)	ns	-0.25*	ns	-0.22*	ns	ns
Bilirubin (*r*)	ns	0.23*	ns	ns	0.22*	-0.32**
T-cholesterol (*r*)	ns	0.22*	0.22*	0.23*	ns	ns
Triglyceride (*r*)	ns	ns	ns	ns	ns	ns
HDL (*r*)	ns	ns	ns	ns	ns	ns
LDL (*r*)	ns	0.32**	0.30*	0.29*	ns	ns
Glucose (*r*)	ns	ns	ns	ns	0.81‡	ns
Fructosamine (*r*)	ns	ns	ns	ns	0.76‡	ns
BUN (*r*)	-0.22*	-0.29*	-0.25*	-0.23*	ns	ns
Creatinine (*r*)	ns	ns	ns	ns	ns	ns

r, correlation coefficient.
ns, no significance.
*, $P<0.05$; **, $P<0.01$; ‡, $P<0.0001$ (significant correlation).

that liver dysfunction lead to an elevation in seru ALT levels and thereby may result in a decrease in hematopoiesis (Wojchowski et al., 2006). However, further studies should be performed for clarifying such association. Pre-OP levels of bilirubin were positively associated with Pre-OP levels of erythrocyte HbAlc, but inversely associated with Pre-OP platelet counts ($P<0.05$). From a physiological point of view, higher counts of erythrocyte probably induce an elevation of serum bilirubin in CAD. Especially, diabetic patients with CAD had a significantly increased levels of erythrocyte aggregation (Jax et al., 2009), resulting in hemolysis and thereby erythropoiesis. In the present study many patients have had diabetes. CAD can generate physical stimuli such as shear stress or hypoxia, leading to hemolysis and microparticles formations (VanWijk et al., 2003). Microparticles are circulating, phospholipid rich, submicron particles released from the membranes of endothelial cells and erythrocytes (Lynch and Ludlam, 2007). The phospholipid properties of microparticles permit them to bind coagulation factors and promote the formation and activity of coagulation enzyme complexes, a role which has traditionally been thought to be provided by activated platelets. Microparticles expressing tissue factor can also be identified in some circumstances, thus providing a suitable environment to both initiate and support coagulation (Lynch and Ludlam, 2007). These phenomena appear to explain a positive or negative relationship of Pre-OP bilirubin levels to Pre-OP erythrocyte or platelet counts in the present study.

Pre-OP levels of total cholesterol with LDL were positively associated with Pre-OP levels of erythrocyte, hemoglobin, or hematocrit ($P<0.05$). The present study can not explain these relationships and thus further studies should be carried out for clarifying the mechanisms. Pre-OP levels of glucose and fructosamine positively related to Pre-OP levels of HbAlc ($P<0.0001$), indicating that increased glucose and fructosamine levels can induce an elevation of HbAlc (True, 2009). Pre-OP levels of BUN, which is a renal marker, had an inverse correlation with total WBC, erythrocyte, hemoglobin, or hematocrit ($P<0.05$), suggesting that renal function is associated with hematopoiesis. Chronic CAD may cause renal insufficiency and (Shlipak et al., 2003) secondarily lead to a decreased erythropoietin production. Erythropoietin is an essential stimulator of erythropoiesis. Therefore, negative correlations between serum BUN levels and hematological factors levels at preoperative period represent that renal insufficiency with an increased BUN levels may be considered to be as a predictor of cardiovascular outcomes (Mann et al., 2001).

Association between hematological factors and echocardiographic variables

Table 6 shows association between Pre-Op levels of hematological factors and Pre-OP echocardiographic variables. Pre-OP levels of total WBC, erythrocyte, hemoglobin, and hematocrit were positively associated with Pre-OP

Table 6. Association between Pre-OP levels of hematological factor and Pre-OP echocardiographic variables

Variable \ Factor	T-WBC	Erythrocyte	Hemoglobin	Hematocrit	HbA1c	Platelet
LVIDD (*r*)	0.26*	0.23*	0.22*	0.23*	ns	ns
LVIDS (*r*)	0.22*	0.29*	0.28*	0.31*	ns	NS
PWD (*r*)	ns	ns	NS	NS	ns	NS
LA dimension (*r*)	0.32*	0.30*	0.26*	0.22*	ns	NS
LA volume (*r*)	0.26*	ns	NS	NS	ns	NS
RVIDD (*r*)	-0.24*	-0.23*	-0.35**	-0.22*	-0.28*	ns
LVEF (*r*)	ns	ns	ns	ns	-0.22*	ns
SLMCA (*r*)	ns	ns	ns	ns	0.21*	ns
SLAD (*r*)	ns	ns	ns	ns	0.22*	NS
SLCX (*r*)	ns	ns	ns	ns	0.30*	ns
SRCA (*r*)	ns	ns	ns	ns	ns	ns
SBP (*r*)	ns	ns	ns	ns	ns	ns
DBP (*r*)	ns	ns	ns	ns	-0.25*	ns

r, correlation coefficient.
ns, no significance.
*, $P<0.05$; **, $P<0.01$ (significant correlation).

levels of LVIDD, LVIDS, or LA dimension ($P<0.05$), suggesting that these hematological factors may be considered to be as predictor of patients outcomes with CAD. CAD may cause a left heart dysfunction. Especially, higher WBC and erythrocyte counts may lead to CAD in the individuals with potential risks such as diabetes, elder age, and/or dyslipidemia (Ahmed et al., 2006; Goswami et al., 2010). Several epidemiological studies have investigated the possible associations between blood rheology and CAD rates (Lowe GDO, 1997). WBC is one of origines which produce proinflammatory cytokines and thus an elevation and activation of WBC can contribute to the development of CAD Pre-OP levels of RVIDD were inversely related with Pre-OP levels of T-WBC, erythrocyte, hemoglobin, hematocrit, or HbAlc ($P<0.05$). Pre-OP levels of HbAlc had a negative relationship with Pre-OP levels of LVEF but positive relationships with Pre-OP levels of SLMCA, SLAD SLCX and DBP ($P<0.05$). These results reflect that hematological factors may influence the development and prognosis of CAD. Finally, the present findings that Pre-OP levels of HbAlc had positive correlations with stenosis degree of several coronary arteries and negative correlation with LVEF suggest can be responsible for the obstruction of coronary artery (resulting in CAD) and thereby a declined LVEF (so called left heart failure).

Association between biochemical indices and echocardiorapic variables

Table 7 shows relationships between Pre-OP levels of biochemical indices and Pre-OP levels of echocardiographic variables. Pre-OP levels of AST were inversely associated with Pre-OP levels LVEF and DBP ($P<0.05$). Pre-OP levels of ALT had negative relationships with Pre-OP levels of RVIDD, LVEF and DBP ($P<0.05$). Pre-OP levels of bilirubin had positive or negative correlations with Pre-OP levels of LVIDD, LVIDS, RVIDD, LVEF, SRCA, and DBP ($P<0.05$, $P<0.01$, or $P<0.0001$). Pre-OP levels of total cholesterol were positively or negatively associated with Pre-OP LVIDS, RVIDD, or SLCX ($P<0.05$). Pre-OP levels of triglyceride had a positive correlation with Pre-OP levels of SLCX ($P<0.05$). Pre-OP levels of HDL were negatively associated with RVIDD, whereas Pre-OP levels of LDL were negatively or positively correlated with RVIDD or SLCX ($P<0.05$). Pre-OP levels of glucose had negative or positive relationships with RVIDD, LVEF, SLAD, or DBP ($P<0.05$ or $P<0.01$), while Pre-levels of fructosamine had positive or negative with LVIDS, PWD, RVIDD, LVEF, SLMCA, SLAD, or SLCX ($P<0.05$, $P<0.01$, or $P<0.001$). Pre-OP levels of BUN were positively or negatively associated with RVIDD or LVEF ($P<0.05$),

Table 7. Association between Pre-OP levels of biochemical indices and Pre-OP echocardiographic variables

Variable \ Index	AST	ALT	BIL	T-CH	TG	HDL	LDL	GLU	BUN	CRE	FRUC
LVIDD (*r*)	ns	ns	0.21*	ns	ns	ns	ns	ns	ns	ns	ns
LVIDS (*r*)	ns	ns	0.22*	0.26*	ns	ns	ns	ns	ns	ns	0.21*
PWD (*r*)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.37**
LA dimension (*r*)	ns	ns	ns	ns	ns	ns	0.22	ns	ns	ns	ns
LA volume (*r*)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
RVIDD (*r*)	ns	-0.33**	-0.50‡	-0.24*	ns	-0.66‡	-0.28*	-0.32**	0.30*	0.57‡	-0.41†
LVEF (*r*)	-0.30*	-0.22*	-0.30*	ns	ns	ns	ns	-0.26*	-0.28*	ns	-0.32**
SLMCA (*r*)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.22*
SLAD (*r*)	ns	ns	ns	ns	ns	ns	ns	0.26*	ns	ns	0.33**
SLCX (*r*)	ns	ns	ns	0.21*	0.24*	ns	0.31*	ns	ns	0.22*	0.31*
SRCA (*r*)	ns	ns	0.29*	ns	ns	ns	ns	ns	ns	ns	ns
SBP (*r*)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
DBP (*r*)	-0.22*	-0.25*	-0.32**	ns	ns	ns	ns	-0.23*	ns	ns	ns

r, correlation coefficient.
ns, no significance.
*, $P<0.05$; **, $P<0.01$; †, $P<0.001$; ‡, $P<0.0001$ (significant correlation).
Abbreviation: BIL, bilirubin; T-CH, total cholesterol; CRE, creatinine; FRUC, fructosamine.

whereas Pre-OP levels of creatinine were positively correlated with RVIDD and SLCX ($P<0.05$ and $P<0.0001$).

These results suggest two possibility in patients with CAD, First, chronic CAD can contribute to secondarily hepatic and/or renal dysfunction, resulting in an association between biochemical markers and echocardiographic variables. Second, biochemical markers may be responsible for the development of CAD, suggesting there is a relationship between biochemical markers and echocardiographic variables.

As is well known, hyperglycemia, increased fructosamine and aminotransferase levels, dyslipidemia, and decreased bilirubin concentration may cause the development of CAD.

Several studies have demonstrated that increased aminotransferases (AST and ALT) were strongly associated with adiposity and other features of metabolic syndrome and that ALT was a predictor for the development of CAD (Schindhelm et al., 2009).

Bilirubin is a potent physiological antioxidant that may provide important protection against atherosclerosis, CAD, and inflammation (Ghem et al., 2010). Bilirubin has a powerful scavenging of peroxyl radicals, which cause lipid peroxidation and inflammation and thereby the development of CAD events. therefore, a decreased bilirubin level is one of several factors that are involved in pathogenesis of CAD (Mylonas and Kouretas, 1999).

Pre-OP levels of fructosamine and bilirubin among biochemical markers were frequently associated with Pre-OP echocardiographic variables. These findings suggest that Pre-OP levels of bilirubin and fructosamine may be considered to be useful and powerful predictors of CAD. An increased fructosamine levels result from hyperglycemia (diabetes), which is a potent pathogenesis of cerebral and cardiovascular accidents.

Association between hematological factors and cardiac markers

Associations between Pre-OP levels of hematological factors and cardiac markers were summarized in Table 8. Pre-OP levels of HbAlc had only a positive relationship with Pre-OP levels of CRP ($P<0.05$). There were no significant relationships between the other factors ($P>0.05$). Some investigations have proposed strong evidence for the importance of primary or secondary inflammatory processes in the pathogenesis of atherosclerosis (de Jong et al., 1997). CRP as a marker of chronic inflammation, is induced by interleukin 1 and 6 (Ikeda et al., 1992). Moreover, Tataru et al. (2000) have recently showed a significant association

between CRP and the severity of atherosclerosis in myocardial infarction patients with stable angina pectoris. Raised HbAlc levels could be an independent risk factor for stroke or CAD in people with and without diabetes (Selvin et al., 2005a). Furthermore, any reduction in HbAlc level is lowest risk being in those with HbAlc values in the normal (<6.0%) (Stratton et al., 2000).

Previous and our studies demonstrate that HbAlc is a very useful marker for the diagnosis and prognosis of CAD due to inflammatory reaction.

Association between biochemical indices and cardiac markers

Association between Pre-OP levels of biochemical indices and Pre-OP cardiac markers were summarized in Table 9. Pre-OP levels of AST ($P<0.0001$) and glucose ($P<0.05$ and $P<0.05$) were positively correlated with cTNI, CK-MB, and CRP, whereas Pre-OP levels of ALT were positively associated with cTNI and CRP ($P<0.05$). Pre-OP levels of bilirubin had positive relationships with cTNI and CK-MB ($P<0.05$), while Pre-OP levels of HDL had a negative correlation with CRP ($P<0.05$). Pre-OP levels of fructosamine were positively associated with BNP and CK-MB, ($P<0.05$) whereas Pre-OP levels of BUN were positively correlated with BNP ($P<0.05$). As earlier mentioned, biochemical indices such as AST, ALT bilirubin, HDL, glucose, fructosamine, and BUN may be useful predictor for the diagnosis and prognosis of CAD. Especially, our data indicate that HDL is a potent antiinflammatory indicator, which protects the development of atherosclerosis.

Association between hematological factors and post-operative variables

Table 10 shows association between hematological factors and postoperative variables.

Pre-OP levels of erythrocyte, hemoglobin, and hematocrit

Table 8. Association between Pre-OP levels of hematological factors and Pre-OP levels of cardiac markers

Marker	BNP	cTNI	CK-MB	CRP
T-WBC (*r*)	ns	ns	ns	ns
Erythrocyte (*r*)	ns	ns	ns	ns
Hemoglobin (*r*)	ns	ns	ns	ns
Hematocrit (*r*)	ns	ns	ns	ns
HbA1c (*r*)	ns	ns	ns	0.25*
Platelet (*r*)	ns	ns	ns	ns

r, correlation coefficient.
ns, no significance.
*, $P<0.05$ (significant correlation).

Table 9. Association between Pre-OP levels of biochemical indices and Pre-OP levels of cardiac markers

Marker	BNP	cTNI	CK-MB	CRP
AST (*r*)	ns	0.57‡	0.58‡	0.43‡
ALT (*r*)	ns	0.27*	ns	0.22*
Bilirubin (*r*)	ns	0.27*	0.29*	ns
T-cholesterol (*r*)	ns	ns	ns	ns
Triglyceride (*r*)	ns	ns	ns	ns
HDL (*r*)	ns	ns	ns	-0.26*
LDL (*r*)	ns	ns	ns	ns
Glucose (*r*)	ns	0.33**	0.23*	0.25*
Fructosamine (*r*)	0.25*	ns	0.21*	ns
BUN (*r*)	0.26*	ns	ns	ns
Creatinine (*r*)	ns	ns	ns	ns

r, correlation coefficient.
ns, no significance.
*, $P<0.05$; **, $P<0.01$; ‡, $P<0.0001$ (significant correlation).

Table 10. Association between Pre-OP levels of hematological factors and postoperative variables

Variable	OP-time	Graft-no.	PMVT	ICU-period	Hospitalization
T-WBC (*r*)	ns	ns	ns	ns	ns
Erythrocyte (*r*)	ns	ns	-0.23*	0.33**	ns
Hemoglobin (*r*)	ns	ns	-0.27*	0.43‡	ns
Hematocrit (*r*)	ns	ns	-0.28*	0.39†	ns
HbA1c (*r*)	ns	0.22*	ns	0.22*	NS
Platelet (*r*)	ns	ns	-0.23*	-0.22*	0.37†

r, correlation coefficient.
ns, no significance.
*, $P<0.05$; **, $P<0.01$; †, $P<0.001$; ‡, $P<0.0001$ (significant correlation).
Abbreviation: OP-time, operation time; Graft-no., number of vessel for CABG surgery; PMVT, postoperative mechanical ventilation time; ICU-period, intensive care unit-staying period.

Table 11. Association Pre-OP levels of biochemical indices and postoperative variables

Variable	OP-time	Graft-no.	PMVT	ICU-period	Hospitalization
AST (*r*)	ns	ns	ns	0.28*	ns
ALT (*r*)	ns	ns	ns	0.22*	ns
Bilirubin (*r*)	ns	ns	0.28*	0.24*	0.22*
T-cholesterol (*r*)	ns	ns	ns	ns	ns
Triglyceride (*r*)	ns	0.23*	ns	0.22*	ns
HDL (*r*)	ns	ns	-0.27*	-0.26*	ns
LDL (*r*)	ns	ns	ns	0.21*	ns
Glucose (*r*)	ns	ns	ns	ns	ns
Fructosamine (*r*)	0.30*	0.44‡	0.25*	ns	ns
BUN (*r*)	ns	ns	ns	ns	0.22*
Creatinine (*r*)	ns	ns	ns	ns	ns

r, correlation coefficient.
ns, no significance.
*, $P<0.05$; ‡, $P<0.0001$ (significant correlation).

were inversely associated PMVT ($P<0.05$), while they were positively correlated with ICU-period ($P<0.01$, $P<0.01$ and $P<0.0001$). Pre-OP levels of HbAlc were positively associated with Graft-number and ICU-period ($P<0.05$), whereas Pre-OP levels of platelet were negatively or positively correlated with PMVT, ICU-period, or hospitalization ($P<0.05$ or $P<0.01$).

These results suggest that some hematological factors may be useful for assessing postoperative outcomes in patients with CAD. However, further study are need to clearly clarify and justify these relationships.

Association between biochemical indices and postoperative variables

Association between biomedical indices and postoperative variables is condensed in Table 11. OP-time had a positive relationship with Pre-OP levels of fructosamine ($P<0.05$). Graft-number was positively associated with Pre-OP levels of triglyceride and fructosamine ($P<0.05$ and $P<0.0001$). PMVT was positively associated with bilirubin and fructosamine ($P<0.05$), but inversely correlated with HDL ($P<0.05$). ICU-period was positively correlated with Pre-OP levels of AST, ALT, bilirubin, triglyceride, and LDL ($P<0.05$), but inversely correlated with HDL ($P<0.05$). Hospitalization was positively associated with Pre-OP levels of bilirubin and BUN ($P<0.05$).

These data reflect that HDL is an important indicator for the prevention of CAD and good postoperative outcomes, and that other biochemical indices may involved in the development of CAD and poor postoperative outcomes.

In conclusion, Pre-OP levels of hematological and biochemical markers might be useful in the diagnosing and prognosing CAD.

REFERENCES

Ahmed W, Orasanu G, Nehra V, Asatryan L, Rader DJ, Ziouzenkova O, Plutzky J. High-density lipoprotein hydrolysis by endothelial lipase activates PPARalpha: a candidate mechanism for high-density lipoprotein-mediated repression of leukocyte adhesion. Circ Res. 2006. 98: 490-498.

Algenstaedt P, Schaefer C, Biermann T, Hamann A, Schwarzloh B, Greten H, Rüther W, Hansen-Algenstaedt N. Microvascular alterations in diabetic mice correlate with level of hyperglycemia. Diabetes 2003. 52: 542-549.

Bancells C, Sánchez-Quesada JL, Birkelund R, Ordóñez-Llanos J, Benítez S. HDL and electronegative LDL exchange anti- and pro-inflammatory properties. J Lipid Res. 2010. 51: 2947-2956.

Benítez S, Camacho M, Bancells C, Vila L, Sánchez-Quesada JL, Ordóñez-Llanos J. Wide proinflammatory effect of electronegative low-density lipoprotein on human endothelial cells assayed by a protein array. Biochim Biophys Acta. 2006. 1761: 1014-1021.

Chen CH, Jiang T, Yang JH, Jiang W, Lu J, Marathe GK, Pownall HJ, Ballantyne CM, McIntyre TM, Henry PD, Yang CY. Low-density lipoprotein in hypercholesterolemic human

plasma induces vascular endothelial cell apoptosis by inhibiting fibroblast growth factor 2 transcription. Circulation 2003. 107: 2102-2108.

de Jong SC, Stehouwer CD, van den Berg M, Vischer UM, Rauwerda JA, Emeis JJ. Endothelial marker proteins in hyperhomocysteinemia. Thromb Haemost. 1997. 78: 1332 -1337.

Dickstein K, Aarsland T, Hall C. Plasma N-terminal atrial natriuretic factor: a predictor of survival in patients with congestive heart failure. J Card Fail. 1997. 3: 83-89.

Ford ES, Giles WH, Mokdad AH. The distribution of 10-Year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. J Am Coll Cardiol. 2004. 43: 1791-1796.

Ghem C, Sarmento-Leite RE, de Quadros AS, Rossetto S, Gottschall CA. Serum bilirubin concentration in patients with an established coronary artery disease. Int Heart J. 2010. 51: 86-91.

Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR Jr, Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989. 79: 8 -15.

Goswami B, Rajappa M, Singh B, Ray PC, Kumar S, Mallika V. Inflammation and dyslipidaemia: a possible interplay between established risk factors in North Indian males with coronary artery disease. Cardiovasc J Afr. 2010. 21: 103-108.

Hall ER, Martin SA, Suzuki JB, Falkler WA Jr. The gingival immune response to periodontal pathogens in juvenile periodontitis. Oral Microbiol Immunol. 1994. 9: 327-334.

Ikeda U, Ohkawa F, Seino Y, Yamamoto K, Hidaka Y, Kasahara T, Kawai T, Shimada K. Serum interleukin 6 levels become elevated in acute myocardial infarction. J Mol Cell Cardiol. 1992. 24: 579-584.

Jax TW, Peters AJ, Plehn G, Schoebel FC. Hemostatic risk factors in patients with coronary artery disease and type 2 diabetes - a two year follow-up of 243 patients. Cardiovasc Diabetol. 2009. 8: 48.

Katus HA, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol. 1991. 67: 1360-1367.

Lee TH, Goldman L. Serum enzyme assays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. Ann Intern Med. 1986. 105: 221-233.

Lee HS, Cheng QL, Thako NV. ECG waveform analysis by significant point extraction. I. Data reduction. Comput Biomed Res. 1987. 20: 410-427.

Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med. 1998. 339: 321-328.

Lowe GDO. Haemostatic risk factors for arterial and venous thrombosis. In: Poller L, Ludlam CA. eds. Recent advancesin blood coagulation, 7th edn. Edinburgh: Churchill Livingstone 1997. 69-96.

Lynch SF, Ludlam CA. Plasma microparticles and vascular disorders. Br J Haematol. 2007. 137: 36-48.

Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001. 134: 629-636.

Medeiros LJ, Gelb AB, Weiss LM. Low-grade renal cell carcinoma. A clinicopathologic study of 53 cases. Am J Surg Pathol. 1987. 11: 633-642.

Mylonas C, Kouretas D. Lipid peroxidation and tissue damage. In Vivo 1999. 13: 295-309.

Nieuwdorp M, Meuwese MC, Vink H, Hoekstra JB, Kastelein JJ, Stroes ES. The endothelial glycocalyx: a potential barrier between health and vascular disease. Curr Opin Lipidol. 2005. 16: 507-511.

Schindhelm RK. Serum alanine aminotransferase, metabolic syndrome, and cardiovascular disease in an Australian population. Am J Gastroenterol. 2009. 104: 2857-2858.

Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation 2003. 107: 87-92.

Singh HS, Bibbins-Domingo K, Ali S, Wu AH, Schiller NB, Whooley MA. N-terminal pro-B-type natriuretic peptide and inducible ischemia in the Heart and Soul Study. Clin Cardiol. 2009. 32: 447-453.

Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993. 16: 434-444.

Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000. 321: 405-412.

Tataru MC, Heinrich J, Junker R, Schulte H, von Eckardstein A,

Assmann G, Koehler E. C-reactive protein and the severity of atherosclerosis in myocardial infarction patients with stable angina pectoris. Eur Heart J. 2000. 21: 1000-1008.

True MW. Circulating biomarkers of glycemia in diabetes management and implications for personalized medicine. J Diabetes Sci Technol. 2009. 3: 743-747.

VanWijk MJ, VanBavel E, Sturk A, Nieuwland R. Microparticles in cardiovascular diseases. Cardiovasc Res. 2003. 59: 277 -287.

Watanabe S, Shite J, Takaoka J, Shinke T, Imuro Y, Ozawa T, Otake H, Matsumoto D, Ogasawara D, Paredes OL, Yokoyama M. Myocardial stiffness is an important determinant of the plasma brain natriuretic peptide concentration in patients with both diastolic and systolic heart failure. Eur Heart 2006. 27: 832-838.

Wojchowski DM, Menon MP, Sathyanarayana P, Fang J, Karur V, Houde E, Kapelle W, Bogachev O. Erythropoietin-dependent erythropoiesis: New insights and questions. Blood Cells Mol Dis. 2006. 36: 232-238.