Can Presence of Toxic Granulation Predict Subsequent Congestive Heart Failure Among Post Coronary Artery Bypass Graft Patients?

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Background --- In post-Coronary Artery Bypass Graft (CABG) patients, congestive heart failure (CHF) is an important factor influencing morbidity and mortality. Studies have shown that cardiopulmonary bypass generates a systemic inflammatory response, including the activation of the complement cascade and leukocytes, contributing to postoperative heart failure. Toxic granulation appears as dark blue black granules in the cytoplasm of neutrophils. It is a stress response to acute infections, severe inflammatory states, burns and drug poisoning. In this study, we would want to establish that the presence of toxic granulation within 24 hours post-CABG is a predictor of CHF in these patients.

Methods --- This is a prospective, cohort study involving patients who underwent elective coronary artery bypass graft surgery at Philippine Heart Center (PHC) between August 2006 and July 2007. Complete blood count obtained within the first 24 hours post-CABG was correlated with the development of CHF (documented with clinical symptoms and confirmed with radiologic and/or echocardiographic findings) within four days after CABG surgery.

Results --- A total of 225 patients were included in the study. The presence of toxic granulation within the first twenty-four hours after CABG surgery was found to be statistically significant predictor of subsequent development of CHF (p value 0.006). Other significant positive predictors of CHF included the presence of a total WBC > 15.3 x 10 9/L (p value 0.01) and high ANC 12.65 ± 3.86 (p value.0.01). Multivariable analysis revealed a significant correlation with the presence of toxic granulation and subsequent post-operative CHF (OR 2.017 p value 0.031).

Conclusion --- The presence of toxic granulation within the first twenty-four hours after elective CABG is associated with subsequent development of CHF. This may help in the identification of high risk patients who might benefit from aggressive management. ***Phil Heart Center J 2008; 14(1):8-13.***

Key Words: Congestive heart Failure ■ Toxic Granulation, Coronary Artery Bypass Graft Surgery

The identification of factors that can be used to predict prognosis of patients who will undergo coronary artery bypass surgery is a continuing challenge. The occurrence of heart failure after coronary bypass surgery is an important factor influencing its morbidity and mortality.

While considerable information has been published on preoperative and intra-operative predictors of operative morbidity and mortality of cardiac surgery, few studies have assessed such predictors of major complications after surgery.

Cardiopulmonary bypass (CPB) activates complement by large blood surface contact area in the extra corporeal circuit.[1] Through either the classic pathway or alternative pathway, C3 is activated and cleaved into two fragments, C3a and C3b; the former is released into plasma, whereas the latter binds to the material surface indicating the amplification pathway of complement activation during CPB. The main consequence of activation of the complement system is considered the subsequent activation of leukocytes that leads to a systemic inflammatory reaction contributing to post operative morbidity after cardiac operations.[2]

The use of cardiopulmonary bypass distinguishes conventional cardiac surgery from other types of surgery. Blood contact with the synthetic surface of bypass equipment results in generally inflammatory response, altered endothelial cell interactions and vasospasm, which may in combination produce low flow states in the microcirculation of the heart, brain or other organs. Left ventricular dysfunction and myocardial

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infarction as well as disruption of normal physiology in a number of organs systems may then ensue.[3]

Toxic granulations are dark course granules found in granulocytes often seen in infection and inflammation. It is thought to be due to impaired cytoplasmic maturation, in the effort to rapidly generate large numbers of granulocytes. Thus, its presence is a sign of overwhelming inflammatory process.[4] Therefore, the purpose of this study is to establish that the presence of toxic granulation is a predictor of congestive heart failure in post coronary artery bypass surgery patients. As a consequence of the overwhelming inflammatory process of the vascular system, microvasculopathy ensues causing low flow circulation to the myocardium. This clinical state leads to a hibernating myocardium. Accumulative evidence suggests that oxidative stress and the release of pro inflammatory mediators/cytokines known to have negative inotropic effects, such as interleukins (IL-6, IL-2, IL-1β) and tumor necrosis factor α during cardiopulmonary bypass surgery probably contribute to the development of congestive heart failure (CHF).5 Therefore, besides severely decreasing flow in the microcirculation, CPB causes the release of proteins directly toxic the heart muscle cells.

With such results, presence of toxic granulations immediately after cardiac surgery may serve as a simple inexpensive, non-invasive marker to identify patients who are high risk for development of CHF. Furthermore, this study will attempt to establish if the Absolute Neutrophilic Count and leukocytosis will truly reflect the myocardial inflammatory response and are associated to the development of CHF post coronary bypass surgery.

Coronary artery bypass graft surgery (CABG) is now commonly performed operation in our institution. Post operative mortality and morbidity has been the primary criterion for judging the quality of surgical outcomes and several models have been developed to predict mortality based on preoperative and intraoperative data. The ability to predict post-operative morbidity and mortality is important to patients, families and physicians.

Leukocytosis and increased Absolute Neutrophil Count (ANC) has been associated with CHF in post Acute Myocardial Infarction patients. Mechanism for association has been postulated that cytokines from neutrophils have a negative inotropic and direct cardiotoxic effect.[7]

In a local study, done by Ypil et. al., they found a strong association between high ANC and congestive heart failure in post AMI patients.

To our knowledge, there is no other study that evaluated toxic granulation and its correlation with CHF in post CABG patients. This study was undertaken to determine if there is a correlation between presence of toxic granulation and development of CHF in patients who undergo post CABG. This study also validated whether toxic granulation is comparable to ANC and leukocytosis as predictor of CHF in post CABG patients.

Methods

Study Design and Selection of Study Population

This was a prospective, cohort study conducted at Philippine Heart Center, a tertiary hospital. Patients with known coronary vessel disease and candidate for elective coronary artery bypass graft surgery were included in this study.

Exclusion criteria were emergency cardiac surgery, history of PCI or CABG, chronic renal disease, history of COPD, previous cardiac surgery, OPCAB surgery, and documented incomplete revascularization.

Data Collection Outcome Measures and Variable Classification

Based on medical history, the following data were obtained age, sex and coronary risk profile (hypertension, diabetes mellitus, smoking history, dyslipidemia, obesity and body surface area). Preoperative ejection fraction by two dimensional echocardiogram and coronary angiogram results were also noted. The total bypass time and total ischemic time were also recorded.

Laboratory results (total WBC count, percentage of neutrophils in the differential count, absolute neutrophil count and presence of toxic granulations) within the first 24 hours after surgery were noted.

Outcomes measures included the development of Congestive Heart Failure (CHF), as described by clinical signs and symptoms with radiologic evidence of pulmonary congestion within four days from surgery. Documented were episodes of CHF that occurred within the first 4 days after surgical intervention. Four days was chosen as the cut off because after this time, the development of CHF may be influenced by therapeutic interventions and/or other post surgical complications and therefore, the blood picture might be less relevant.[7]

The variables were dichotomized as follows: sex (male vs female); hypertension, diabetes mellitus, smoking history, dyslipidemia, obesity; toxic granulations and leukocytosis. (presence vs. absence). Age, absolute neutrophilic count, preoperative ejection fraction and total bypass and ischemic time were recorded as continuous variables.

Statistical Analysis

Data were encoded and analyzed in SPSS version 13 for windows. Descriptive statistics were generated for all variables. For all nominal and ordinal data, frequency and percentages were generated, while mean and standard deviation for continuous variables were used. Associations of the different variables with CHF were done using the following statistics tests. Chi square test was used to compare / associate nominal data. Student T test was used to compare two groups with numerical data (compares means). Mann Whitney U test is a non parametric equivalent of t- test used to compare two groups with numerical data (compares medians instead of means). Logistic regression analysis is a multivariate test used to identify predictors of certain outcome where both the independent and dependent variables are dichotomized.

The sample size calculation was performed using estimation about a proportion. We determined that a minimum of 129 patients were necessary to conduct this study.

Results

Baseline Characteristics

A total of 305 patients who were admitted for coronary bypass surgery were screened between August 2006 and July 2007. A total of eighty patients were excluded: 15 patients were excluded for they underwent emergency coronary surgery bypass; 10 patients had incomplete surgical revascularization; 8 had off pump CABG (OPCAB); 8 had previous cardiac surgery which required reopening of the pericardium; 10 had elevated serum creatinine > 0.20 mol/L preoperatively; 8 had Chronic Pulmonary disease; and 21 patients had major cardiac procedures done other than or in addition to CABG.

Complete revascularization was accomplished if technically feasible with saphenous vein grafts and internal mammary arteries. Standard surgical techniques were used with patients under hypothermic arrest with blood cardioplegia. No off pump CABG surgery was included. A final cohort of two hundred twenty five patients was included in this study.

Table 1 shows the clinico-demographic characteristics of the included patients. The study cohort was predominantly male (85.3%) with a mean age of 59.76 ± 9.18 years (range 35 - 78). Mean body surface of 1.77 ± 0.15 m2 (range 1.39 – 2.30). The median length of hospital stay prior to CABG was 4.54 ± 4.09. Majority of the patients were hypertensive (71.6%) and diabetics (41.3%). A number of patients had smoked cigarettes 75 (33.3%).

Table 1. Clinico-demographic characteristics of included subjects

Characteristics	Frequency (%) N=225	Mean (SD)
Age (years)		59.76 ± 9.18
Male Sex	192 (85.3)	
Weight (kg)		68.98 ± 10.87
Body surface area (m^2)		1.77 ± 0.15
Diabetes Mellitus	93 (41.3)	
Hypertension	161 (71.6)	
Smoker (previous and current)	75 (33.3)	
Dyslipidemia	91 (40.4)	
Obesity	38 (16.9)	
Length of hospital stay (days)		4.54 ± 4.09

Univariate predictors of CHF

In 62 (27.5%) patients, CHF developed within the first four days of post CABG, documented as clinical signs and symptoms compatible with the diagnosis of CHF. Among this patients, 57 (92%) had radiologic evidence of pulmonary congestion and pulmonary edema and 5 (18%) had echocardiographic findings of systolic dysfunction (EF < 40%). Twenty eight (39.4%) of them had toxic granulation within the first day of post CABG.

The presence of toxic granulation within the first twenty-four hours after CABG surgery was found to be highly significant predictor of subsequent development of CHF. Other significant positive predictors of CHF included the presence of a total WBC > 15.3 x 10 9/L. and high ANC 12.65 ± 3.86. (Table 2 and 3).

Multivariable Analysis

The presence of a toxic granulation remained significantly associated with subsequent development of CHF even after adjusting for other significant predictors. (Table 4).

Discussion

The results of this study suggest that the presence of toxic granulations (dark course granules found in granulocytes) within the 24 hours post CABG surgery is strongly associated with early development of CHF post cardiac surgery.

Although most patients tolerate cardiopulmonary bypass well, a number of studies have established a cardiopulmonary leak syndrome associated with fever, leukocytosis, renal dysfunction and a bleeding diathesis. These multi-organ effects have been called the "post pump syndrome".[8-9] The mechanism for this syndrome may be related to the exposure of blood to non-endothelial surfaces causing subsequent complement activation, platelet aggregation and effects on

fibrinolytic system.[10-11]

Kawamura et. al. investigated myocardial injury determined by increase in creatine phosphokinase, neutrophils and granulocytes in adult patients undergoing cardiac surgery and cardiopulmonary bypass,[12] because interleukin 8 is chemotactic for these cells, it has been suggested that it activates neutrophils.[13]

They proposed that increase in interleukin 6 and interleukin 8 one hour after reperfusion are responsible for neutrophil activation and cell injury. Interleukin 6 also plays an important role in inflammation. Other investigators have also demonstrated elevation of other interleukins following cardiac surgery and cardiopulmonary bypass.[14]

Table 2. Association of variables to development of CHF post-CABG surgery

Variables	Presence of CHF n-62	Absence of CHF n-163	p-value
Age (years)	61 ± 9.62	59 ± 9.00	0.243 (NS)
Male Sex	53 (85.5)	139 (85.3)	0.864 (NS)
BSA (m^2)	1.76 ± 0.14	1.77 ± 0.16	0.717 (NS)
DM	25 (40.3)	68 (41.8)	0.969 (NS)
HPN	45 (72.5)	116 (71.1)	0.964 (NS)
Smoker	20 (32.2)	55 (33.7)	0.958 (NS)
Dyslipidemia	26 (41.9)	65 (39.8)	0.897 (NS)
Obesity	10 (16.1)	28 (17.1)	0.991 (NS)
WBC Count	14.86 ± 4.29	13.70 ± 4.30	0.01*
Pre-operative Ejection Fraction	57.32±14.82	56.06±13.06	0.53 (NS)
Total Ischemic Time (hours)	1.69±0.67	1.68±0.49	0.61 (NS)
Total Bypass Time (hours)	2.32±0.74	2.33±0.65	0.93 (NS)
Number of diseased vessel			0.74 (NS)
1	0	3 (1.8)	
2	10 (16.1)	20 (12.3)	
3	52 (83.9)	140 (85.9)	
Number of vessel Graft(s) used			0.576 (NS)
1	0	2 (1.2)	
2	2 (3.2)	7 (4.2)	
3	19 (30.6)	45 (27.6)	
4	32 (52.6)	74 (45.3)	
5	8 (12.9)	30 (18.4)	
6	1 (1.6)	5 (3.0)	

*significant

Table 3. Validity of Absolute Neutrophil Count (ANC), Presence of Toxic Granulation, Leukocytosis and White Blood Cell Count in Predicting Congestive Heart Failure post-CABG

Parameter	Presence of CHF (n-62)	Absence of CHF (n-163)	p-value	Sn*	Sp*	PPV*	NPV*	Kappa
ANC (mean, SD)	12.65 (3.89)	11.09 (3.88)	0.01**	87.1	25.2	30.7	83.7	0.078
Toxic Granulation			0.006**	45	73.6	39.4	77.9	0.078
(+)	28 (39.4)	43 (60.6)						
(-)	34 (22.1)	120 (77.9)						
Leukocytosis			0.04**	88.7	23.3	30.6	84.4	0.180
(+)	55 (30.6)	125 (69.4)						
(-)	7 (15.6)	38 (84.4)						

Sn* Sensitivity PPV* Positive Predictive Value Sp* Specificity NPV*Negative Predictive Value
** significant

Table 4. Factors Predictive of CHF by Multivariate Analysis

	B	SE	OR*	P value	Significance
DM	-0.031	0.323	0.969	0.923	NS
HPN	0.059	0.345	1.060	0.865	NS
Smoking History	-0.088	0.334	0.916	0.791	NS
DYSLIPIDEMIA	0.115	0.315	1.122	0.715	NS
OBESITY	-0.141	0.420	0.868	0.737	NS
TOXIC GRANULATION	0.702	0.325	2.017	0.031	**
LEUKOCYTOSIS	0.653	0.462	1.92	0.158	NS
Constant	-1.783	0.533	0.168	0.001	**

OR* odds ratio
** Significant

In our study, standardized systemic heparinization was applied before cardiopulmonary bypass. Although we are able to antagonize the coagulation cascade with systemic heparinization, we are still unable to prevent the associated inflammatory responses associated with cardiopulmonary bypass.[15]

It is previously noted that older age is a predictor of increased risk after CABG.[16] However, in this study, we demonstrated no significant difference between age group and development of CHF.

It has been well established that the duration of cardiopulmonary bypass has some relationship to postoperative problems. Acute lung injury occurs more frequently when cardiopulmonary bypass period exceeds 150 minutes.[9] However, in this study, we failed to demonstrate the significant relationships between ischemic and bypass time to the development of congestive heart failure.

Cigarette smoking was previously shown to be associated with leukocytosis and risk of ischemic events.[17] However, our study had not shown its association with toxic granulation and leukocytosis with risk of developing CHF.

This study has several limitations. It only included patients for elective CABG. Another limitation of this study is that toxic granulation, ANC and white blood cell count were measured at only one point in time, and this point (although within 24 hours after CABG surgery) was not consistent in all patients studied. Serial monitoring might be more helpful in identifying high-risk individuals.

Measurements and correlations with other markers of myocardial injury and neutrophil activation such as C reactive protein, myeloperoxidase, cardiac MB's and interleukin levels could give a more complete picture of the inflammatory process.

Conclusion

Despite these limitations, the current study demonstrated a significant association between the presence toxic granulations within the first twenty-four hours after elective CABG and subsequent development of CHF within four days after bypass surgery.

The results suggest that presence of toxic granulations may serve as a simple, non-invasive marker to identify patients who are at high risk for development of CHF after CABG surgery

Appendix

Standardized Criteria and Definitions of Variables

Emergency operation: Operation performed immediately to prevent death. It is carried out or referred before the next working days.

Chronic renal insufficiency: History of chronic renal disease or serum creatinine > 0.20mmol/L, or both.

Reoperation: Any prior cardiac surgery

Chronic obstructive pulmonary disease: Pulmonary disease that results in functional disability or requires bronchodilator therapy and/or result in abnormal spirometry, as defined by a forced expiratory volume in 1 s, <75% of that predicted.

Congestive heart failure: Documented history of or treatment for heart failure and/or clinical evidence of heart failure, as defined by an S3 gallop, jugular venous distention, pleural effusion, pulmonary edema, peripheral edema or radiographic evidence of interstitial edema (flash pulmonary edema excluded)

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