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Inflammatory Gene Polymorphisms and Risk of Postoperative Myocardial Infarction After Cardiac Surgery

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Abstract

Background—The inflammatory response triggered by cardiac surgery with cardiopulmonary bypass (CPB) is a primary mechanism in the pathogenesis of postoperative myocardial infarction (PMI), a multifactorial disorder with significant inter-patient variability poorly predicted by clinical and procedural factors. We tested the hypothesis that candidate gene polymorphisms in inflammatory pathways contribute to risk of PMI after cardiac surgery.

Methods and Results—We genotyped 48 polymorphisms from 23 candidate genes in a prospective cohort of 434 patients undergoing elective cardiac surgery with CPB. PMI was defined as creatine kinase-MB isoenzyme level ≥10 × upper limit of normal at 24 hours postoperatively. A 2-step analysis strategy was used: marker selection, followed by model building. To minimize false-positive associations, we adjusted for multiple testing by permutation analysis, Bonferroni correction, and controlling the false discovery rate; 52 patients (12%) experienced PMI. After adjusting for multiple comparisons and clinical risk factors, 3 polymorphisms were found to be independent predictors of PMI (adjusted $P < 0.05$; false discovery rate < 10%). These gene variants encode the proinflammatory cytokine interleukin 6 (*IL6* −572G > C; odds ratio [OR], 2.47), and 2 adhesion molecules: intercellular adhesion molecule-1 (*ICAM1* Lys469Glu; OR, 1.88), and E-selectin (*SELE* 98G > T; OR, 0.16). The inclusion of genotypic information from these polymorphisms improved prediction models for PMI based on traditional risk factors alone (C-statistic 0.764 versus 0.703).

Conclusions—Functional genetic variants in cytokine and leukocyte–endothelial interaction pathways are independently associated with severity of myonecrosis after cardiac surgery. This may aid in preoperative identification of high-risk cardiac surgical patients and development of novel cardioprotective strategies.

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cardiopulmonary bypass; genetics; inflammation; myocardial infarction; single nucleotide polymorphisms

Despite substantial advances in surgical, cardioprotective, and anesthetic techniques, the incidence of perioperative myocardial infarction (PMI) after cardiac surgery remains at 7% to 15%[1] and is associated with reduced long-term survival.[2] PMI is a multifactorial disorder with significant inter-patient variability poorly predicted by clinical and procedural factors, suggesting a possible genetic component.

One of the primary mechanisms in the pathogenesis of perioperative myonecrosis is the complex acute inflammatory response to cardiac surgery with cardiopulmonary bypass (CPB). The extent of perioperative systemic inflammation and associated morbidity and mortality have been related to a variety of environmental stimuli including direct surgical trauma, bioincompatibility of the extracorporeal perfusion circuit, endotoxemia, and multi-organ system ischemia-reperfusion injury.[3] However, increased evidence for heritability of the pro-inflammatory state suggests that individual genetic background also modulates the magnitude of postoperative systemic inflammatory response after cardiac surgery.[4] Therefore, we tested the hypothesis that single nucleotide polymorphisms (SNPs) in candidate genes regulating inflammatory pathways are associated with the incidence of postoperative myocardial infarction in a cohort of patients undergoing cardiac surgery with CPB.

Methods

Patient Population

We studied prospectively collected DNA samples from a cohort of 434 patients undergoing elective cardiac surgery with CPB between September 1997 and May 2002, in whom serial perioperative serum levels of creatine kinase-MB isoenzyme (CK-MB) were measured. All patients were participants in the Perioperative Genetics and Safety Outcomes Study (PEGASUS), an ongoing Institutional Review Board-approved, prospective, longitudinal study at Duke University Medical Center, and provided informed consent. Exclusion criteria were history of renal failure, active liver disease, bleeding disorders, autoimmune diseases, or immunosuppressive therapy. Intraoperative anesthetic, perfusion, and cardioprotective management was standardized, with fentanyl/isoflurane anesthesia, nonpulsatile CPB (30°C to 32°C), crystalloid prime, pump flow rates > 2.4 L/min per m^2, cold blood cardioplegia, α-stat blood gas management, heparin to maintain activated clotting times > 450 seconds, ε-aminocaproic acid infusion, and serial hematocrits kept ≥0.18 during CPB.

Measurement of CK-MB

Serum was collected for measurement of CK-MB levels at baseline and 4.5, 24, and 48 hours after aortic cross-clamp removal, and immediately frozen at − 80°C until analysis. CK-MB levels (mass assays) were determined using a forward immunometric assay at a core laboratory (Biosite Diagnostics, San Diego, Calif). The upper limit of normal (ULN) for CK-MB values at this laboratory is 5 ng/mL.

Definition of Myocardial Injury Phenotype

Recent receiver-operator characteristic analyses from several large cardiac surgery trials have identified a cutoff value of 10-times the ULN for postoperative CK-MB to result in optimal specificity (85%) and sensitivity (39%) for 6-month mortality.[5] Based on these findings and the American College of Cardiology recommendations,[6] PMI was defined as CK-MB serum

concentration exceeding 50 ng/mL (ie, 10-times the ULN for the reference laboratory) at 24 hours postoperatively. This time point was chosen to exclude early enzyme peaks, previously associated with a washout phenomenon.[7]

Candidate Genes and Polymorphisms Selection

Twenty-three candidate genes involved in the pathogenesis of inflammation and myocardial ischemia-reperfusion injury were selected a priori based on previous transcription profiling in humans[8,9] and animal models,[10] pathway analysis,[11] a review of linkage and association studies reported in the literature, and expert opinion. Forty-eight single nucleotide polymorphisms (SNPs) were subsequently selected in these process-specific candidate genes, based on literature review, genomic context,[12] and predictive analyses[13] with an emphasis on functionally important variants (Table 1).

Genotype Analysis

Genotyping was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on a Sequenom™ system (Sequenom, San Diego, Calif) at a core facility (Agencourt Bioscience Corporation, Beverly, Mass). Primers used and polymorphism details can be found at http://anesthesia.duhs.duke.edu/pegasus/. Genotyping accuracy was validated at > 99% by scoring a panel of 6 SNPs in 100 randomly selected patients using an ABI 3700 capillary sequencer (Applied Biosystems, Foster City, Calif).

Statistical Analysis

Before evaluating the contribution of genetic factors, the relationship between traditional risk factors (Table 2) and PMI was explored by multivariable logistic regression (clinical model). We chose the most parsimonious set of significant factors by forward selection and used 100 bootstrap samples for model validation.

For each polymorphism, allele and genotype frequencies were calculated and Hardy-Weinberg equilibrium evaluated using an exact test among unaffected patients. The association between 48 candidate gene polymorphisms and incidence of PMI was tested using a 2-stage analysis approach: marker selection, followed by modeling of genotype–phenotype relationships.[14] Allelic associations with incident PMI were first assessed using χ^2 tests for each of the 48 polymorphisms, and a set of influential markers selected based on nominal $P < 0.1$. To avoid assumptions regarding the modes of inheritance, all analyses were performed using additive (homozygote major allele versus heterozygote versus homozygote minor allele), dominant (homozygote major allele versus heterozygote + homozygote minor allele), or recessive (homozygote major allele plus heterozygote versus homozygote minor allele) models for each polymorphism. Second, we performed multivariable logistic regression analyses to sequentially test main effects and interactions for all pairs followed by 3-way combinations of markers selected in the previous step on incidence of PMI (multi-locus genetic models).

Polymorphism combinations selected by logistic regression were finally entered into a model adjusting for traditional risk factors (clinicogenetic model). The genetic contribution to model fit was tested with a multiple-degree of freedom Wald χ^2 test. In addition, to compare the efficacy of PMI risk prediction models based on clinical and genetic information versus models based on traditional risk factors alone, we computed Akaike's Information Criterion, which adjusts for the number of terms in the multivariable models, and the C-statistic, representing the area under the receiver operator characteristic curve. Population stratification was investigated by genotyping a panel of 54 unlinked null SNPs and computing a scaling factor for adjusting the χ^2 test statistic in 100 bootstrap samples.[15] Furthermore, self-reported ethnicity was tested as a covariate in multiple logistic regression models.[16]

Because the analysis strategy used many separate tests of independence, we used several approaches to account for multiple comparisons. In the genetic model selection process, permutation testing (4000 samples) was used to adjust probability values in pair-wise SNP logistic regressions,[17] and Bonferroni correction to adjust overall genetic model probability values. In addition, we used false discovery rate analysis of all candidate SNPs to estimate and control the proportion of errors among the rejected hypotheses.[18]

All statistical analyses were performed using SAS/Genetics version 9.1 (SAS Inc, Cary, NC). Continuous variables were described as mean ± standard deviation; categorical variables were described as percentages. Adjusted $P < 0.05$ (Bonferroni correction or permutation testing) were considered significant.

Statement of Responsibility

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Of the 434 patients with complete genotype–phenotype data, PMI developed in 52 (12%). Consistent with previous studies, duration of aortic cross-clamping, number of coronary grafts, and history of previous cardiac surgery were identified as independent predictors of postoperative myonecrosis in our population (Table 3).

Among the 48 candidate polymorphisms examined, 4 deviated from Hardy-Weinberg equilibrium in both the white unaffected and PMI groups, and were excluded from subsequent analyses. A set of 11 SNPs was identified based on nominal univariable $P < 0.1$ for association with incident PMI, in any mode of inheritance (Table 4).

After our conservative analysis strategy, 3 marker associations remained significant after full adjustment for multiple comparisons and traditional risk factors: the additive effect of −572G > C interleukin-6 (*IL6*) polymorphism, the additive effect of Lys469Glu intercellular adhesion molecule 1 (*ICAM1*) polymorphism, and the dominant effect of 98G> T E-selectin (*SELE*) polymorphism. Specifically, in multivariable logistic regression models evaluating all possible pairwise and subsequent 3-way SNP combinations, the *IL6* −572G > C (odds ratio [OR], 2.47; 95% confidence interval [CI], 1.02 to 5.97; $P = 0.045$), the *ICAM1* Lys469Glu (OR, 1.88; 95% CI, 1.17 to 3.04; $P = 0.009$), and the *SELE* 98G > T (OR, 0.16; 95% CI, 0.03 to 0.74; $P = 0.019$) polymorphisms were independent predictors of PMI. Collectively, these 3 SNPs resulted in a model with a Bonferroni-adjusted $P = 0.01$, and a C-statistic of 0.695 (Table 3). Importantly, these polymorphisms were also individually significant after controlling the false discovery rate at 10% (Table 4). In a model of PMI risk combining both genetic and clinical factors, the contribution of these 3 polymorphisms remained highly significant ($P = 0.007$), over and above the information provided by traditional risk factors alone. The C-statistic of the final clinicogenetic model based on the *IL6*, *ICAM1*, and *SELE* polymorphisms was 0.764 compared with 0.703 in the clinical-only model, suggesting a gain in discriminatory accuracy (Table 3).

In addition to the 3 polymorphisms significant in the false discovery rate analysis, 3 others were found to be associated with PMI in multivariable logistic regression models with Bonferroni-adjusted $P < 0.05$. These included the 1846C > T polymorphism in C-reactive protein (*CRP*), 19983T > C polymorphism in lipopolysaccharide-binding protein (*LBP*), and −844T > C polymorphism in the catalase (*CAT*) gene (Tables 4 and 5).

In multivariable risk factor-adjusted analyses we found no evidence for an interaction between any of these genetic polymorphisms and self-reported race in explaining incident PMI.

Moreover, in analysis of 54 unlinked markers, the mean (standard error) χ^2 value over 100 bootstrap samples was 0.989 (0.02), suggesting that no cryptic population substructure was present in these data.

Discussion

Despite well-described associations between genetic variation and susceptibility to myocardial infarction among ambulatory populations, there is a paucity of data regarding the occurrence of similar relationships with perioperative myocardial injury in cardiac surgical patients. In this initial report from a prospective cohort study of patients undergoing cardiac surgery with CPB, we found 3 inflammatory polymorphisms to be associated with incident PMI, after adjustment for multiple comparisons. Both risk and protective alleles were identified. These findings add to previous data implicating plasma levels of several cytokines, cell adhesion molecules, and other inflammatory mediators as key determinants of risk of perioperative myocardial injury,[3] suggesting that the products of these genes may represent important targets in preventing perioperative myonecrosis after cardiac surgery.

For interleukin-6 (*IL6*), the encoded protein is a major proinflammatory cytokine involved in the acute inflammatory response to CPB.[3] Polymorphisms in the promoter of *IL6* gene (−572G > C and −174G > C) have been associated with significantly higher postoperative plasma IL-6 levels[19] and prolonged hospitalization after cardiac surgery with CPB.[20]

Intercellular adhesion molecule-1 (ICAM1) is an important adhesion molecule mediating the interaction between activated leukocytes (CD11b) and endothelial surfaces. The non-conservative Lys469Glu polymorphism in *ICAM1* gene, located in an immunodominant epitope involved in integrin-mediated B-cell adhesion and neutrophil transmigration, has been associated with a variety of pro-inflammatory phenotypes like transplant rejection and vasculopathy, vascular restenosis, and multiple sclerosis.[21] These findings are consistent with the observed relationship between the number of Glu469 alleles and incidence of PMI identified in the current study.

With regard to E-selectin, this endothelial membrane protein, also called ELAM1, is expressed by cytokine-stimulated endothelial cells and mediates accumulation/adhesion of leukocytes at sites of inflammation and endothelial damage, implicated in inflammatory injury after cardiac surgery with CPB.[3] Genetic variants in E-selectin have been reported as risk factors for premature/severe coronary artery disease, and are associated with altered leukocyte binding and soluble E-selectin release,[22,23] suggesting a similar functional role in modulating perioperative myonecrosis.

Three additional polymorphisms were also found to be associated with incident PMI at nominal significance levels. One of these, a 1846C > T polymorphism in the 3′-untranslated region of the C-reactive protein (*CRP*) gene, has been associated with altered plasma CRP levels and increased risk of cardiovascular events.[24] The current data thus provide additional support to previous reports implicating CRP as a mediator of tissue damage in acute myocardial ischemia.[25] We also found a 326T > C polymorphism in the lipopolysac-charide-binding protein (*LBP*) gene to be associated with incidence of PMI, an intriguing finding because endotoxin peaks at 4 to 24 hours after CPB, and has been implicated in modulating acute myocardial injury. Finally, the −844T > C polymorphism in catalase (*CAT*) gene associated with protection against PMI is located in the consensus sequence of several transcription factor binding sites; this suggests that allele-specific differential binding of transcription factors may influence gene expression levels and overall antioxidant activity, thus buffering the oxidative stress characteristic of myocardial ischemia-reperfusion injury. Although these latter results are intriguing, more data are needed to provide statistical support for an association.

The specific criteria for defining PMI in the setting of cardiac surgery are still subject to debate, because postoperative biomarker elevations can be caused by several nonischemic etiologies like surgical trauma (atrial cannulation, sewing needles) and manipulation of the heart. However, regardless of causation or the diagnostic cutoff used, it should be emphasized that the biomarker evidence of myonecrosis after cardiac surgery has been consistently associated with an increase in adverse clinical outcomes.[6]

When interpreting any genetic association study, several epidemiological limitations potentially leading to false-positive findings should be considered, including inadequate sample size, selection of control groups, multiple testing, and population stratification. With regard to these concerns, strengths of our study include a relatively large population of cardiac surgery patients and a prospective cohort design that reduces the selection bias inherent in case-control studies. It is possible that the SNPs identified as associated with PMI are in linkage disequilibrium with other functional (causal) variants not included in this study. A much larger study incorporating many more SNPs might be necessary to delineate this effect. Further, we found no race effect in multivariable regression models, and genomic control analysis revealed no evidence of population stratification in these data. Finally, we adjusted for multiple comparisons using several different techniques (permutation testing, Bonferroni correction, false discovery rate), and are presenting all data simultaneously rather than focusing on any one specific finding.

Conclusions

Genetic variants in cytokine and leukocyte–endothelial interaction pathways are independently associated with severity of myonecrosis after cardiac surgery. These initial findings suggest that genetic epidemiological studies can assist in evaluating perioperative morbidity and, if corroborated in other populations, provide insight into preoperative identification of high-risk cardiac surgical patients. Future clinical trials investigating efficacy of novel cardioprotective strategies on cardiac biomarker release may have to be conducted in genotype-stratified patient populations.

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TABLE 1

Genetic Polymorphisms Evaluated in the Study

Gene (Symbol)	Nucleotide Substitution	Genomic Context	SNPid*	Cytogenetic Locus	Minor Allele Frequency (unaffected)
Bactericidal/permeability-increasing protein (BPI)	270T > C	Val16Ala	rs1341023	20q11.23-q12	0.4755
Catalase (CAT)	−844C > T	5“UTR	rs769214	11p13	0.3485
	−262C > T	5”UTR	rs1001179		0.1915
	−21A > T	5′UTR	rs17880664		0.372
Cathepsin G (CTSG)	2108A > G	Asp125Ser	SNP014†	14q11.2	0.0812
CD14 Antigen (CD14)	−260C > T	5′UTR	rs2569190	5q31.1	0.4754
C-reactive protein (CRP)	1059G > C	Leu184Leu	rs1800947	1q21-q23	0.072
	1846 C > T	3′UTR	rs1205		0.3116
Endothelial nitric oxide synthase (NOS3)	−786T > C	5′UTR	rs2070744	7q36	0.3551
	894G > T	Glu298Asp	rs1799983		0.3179
	20628G > T	Intron	rs1799985		0.3121
E-selectin (SELE)	98G > T	5′UTR	rs1805193	1q23-q25	0.1088
	561A > C	Ser149Arg	rs5361		0.093
	1839C > T	Leu575Phe	rs5355		0.0583
Heat shock protein 70-homologous (HSPA1L)	1478C > T	Thr493Met	rs2227956	6p21.3	0.179
	1804G > A	Glu602Lys	rs2075800		0.2463
Intercellular adhesion molecule-1 (ICAM1)	778G > A	Gly241Arg	rs1799969	19p13.3-	0.0891
	1112C > T	Pro352Leu	rs1801714	p13.2	0.0281
	1462A > G	Lys469Glu	rs5498		0.3631
Interleukin 1-alpha (IL1A)	−889C > T	5′UTR	rs1800587	2q14	0.3244
	10876G > T	Ala114Ser	rs17561		0.2997
Interleukin 1-beta (IL1B)	−511T > C	5′UTR	rs16944	2q14	0.3546
	5810G > A	Intron	rs1143633		0.3171
	5887C > T	Phe105Phe	rs1143634		0.2123
Interleukin 1-receptor antagonist (IL1RN)	13760T > C	Ala39Ala	rs2229235	2q14.2	0.2767
	16857T > C	Ser112Ser	rs315952		0.3023
Interleukin 6 (IL6)	−597G > A	5′UTR	rs1800797	7p21	0.4351
	−572G > C	5′UTR	rs1800796		0.0447
	−174G > C	5′UTR	rs1800795		0.4412
Interleukin 8 (IL8)	−251A > T	5′UTR	rs4073	4q12-q13	0.4671
Interleukin 10 (IL10)	−819C > T	5′UTR	rs3021097	1q31-q32	0.27
	−592C > A	5′UTR	rs1800872		0.2644
Lipopolysaccharide-binding protein (LBP)	19983T > C	Pro97Pro	rs2232582	2q11.23-q12	0.1516
	42711T > C	Phe436Leu	rs2232618		0.1017
Platelet-endothelial cell adhesion molecule-1 (PECAM1)	1688G > A	Ser563Asn	rs12953	17q23	0.3613
P-selectin (SELP)	−1969A > G	5′UTR	rs1800805	1q23-q25	0.4195
	1087G > A	Ser331Asn	rs6131		0.1943
	1902A > G	Asn603Asp	rs6127		0.3576
	2013G > T	Val640Leu	rs6133		0.1393
	2361A > C	Thr756Pro	rs6136		0.1179
Superoxide dismutase 3 (SOD3)	760C > G	Arg231Gly	rs1799895	4pter-q21	0.0066
Toll-like receptor 4 (TLR4)	896A > G	Asp299Gly	rs4986790	9q32-q33	0.0634
	1196C > T	Thr399Ile	rs4986791		0.0888
Thrombomodulin (THBD)	1959C > T	Ala473Val	rs1042579	20p11.2	0.1804
Tumor necrosis-alpha (TNFA)	−308G > A	5′UTR	rs1800629	6p21.3	0.1628
	−238G > A	5′UTR	rs361525		0.0418
	1078G > A	Intron	rs1800610		0.0672
Vascular cell adhesion molecule-1 (VCAM1)	−1594T > C	5′UTR	rs1800821	1p32-p31	0.1705

*From NCBI’s dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/).

†Duke internal polymorphism ID number.

UTR indicates untranslated region.

TABLE 2

Demographic, Clinical, and Procedural Characteristics of the Study Population

Characteristics	PMI (n = 52)	No PMI (n = 382)	P*
Age, y	63.7 (11.1)	62.1 (11.1)	0.31
Female, %	32.7	34.2	0.88
History of MI, %	38.5	40.8	0.77
Unstable angina, %	63.0	61.7	0.87
Congestive heart failure, %	17.4	23.8	0.36
Diabetes, %	36.5	29.2	0.33
Hypertension, %	63.5	62.1	0.88
History of stroke, %	4.3	2.9	0.64
Peripheral vascular disease, %	15.2	13.3	0.82
Body surface area, m^2	2 (0.2)	2 (0.2)	0.56
Body mass index, kg/m^2	29 (5)	29 (6)	0.66
LVEF, %	53 (13)	53 (12)	0.76
Preoperative hematocrit, %	39.5 (4.3)	38.8 (8.4)	0.39
Parsonnet risk score	11.5 (9.7)	8.6 (7.4)	0.07
No. of grafts	3 (1.5)	2.6 (1.3)	0.07
Duration of CPB, min	154 (57)	124 (54)	< 0.0001
Duration of cross-clamp, min	95 (44)	69 (35)	< 0.0001
Procedure			
CABG, %	76.9	81.3	0.22
CABG + valve, %	11.5	5.3	
Valve, %	11.5	13.4	
Redo CABG, %	13.0	3.7	0.02
Intraoperative inotropes, %	26.9	12.5	0.008
Self-reported ethnicity:			
African American	11.5	10.3	0.34
European American	80.8	85.8	
Native American	7.7	3.2	
Other	0.0	0.8	

Values expressed as mean (SD) or as %.

*Wilcoxon rank-sum (continuous variables); exact Pearson χ^2 (categorical variables).

LVEF indicates left ventricular ejection fraction; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting.

TABLE 3

Results of Multivariable Logistic Regression Models Using Clinical-Procedural Risk Factors and Genotypic Information

Predictor	OR (95% CI)	Predictor *P*	Model *P*	Model C-statistic	Model AIC
Clinical Model					
AXC time (10 min)	1.17 (1.09–1.26)	< 0.0001	< 0.0001	0.703	367
No. coronary grafts	1.35 (1.09–1.66)	0.005			
Previous cardiac surgery	2.62 (1.11–6.19)	0.027			
Multi-Locus Genetic Model					
IL6 –572G > C (rs1800796)	2.75 (1.2–6.3)	0.017	0.01*	0.695	268
ICAM1 K469E (rs5498)	1.82 (1.17–2.85)	0.009			
SELE 98G > T(rs1805193)	0.19 (0.05–0.81)	0.025			
Clinico-Genetic Model					
AXC time (10 minutes)	1.16 (1.07–1.26)	0.0002	< 0.0001	0.764	251
No. coronary grafts	1.29 (1.002–1.65)	0.048			
Previous cardiac surgery	3.93 (1.21–12.81)	0.023			
IL6 – 572G > C (rs1800796)	2.47 (1.02–5.97)	0.045			
ICAM1 K469E (rs5498)	1.88 (1.17–3.04)	0.009			
SELE 98G > T(rs1805193)	0.16 (0.03–0.74)	0.019			

* Bonferroni-adjusted for n = 136 independent tests (55 2-SNP models, 81 3-SNP models).

C-statistic indicates area under the receiver operator characteristic curve; AIC, Akaike's Information Criterion.

TABLE 4

Estimated Effects of Polymorphisms Selected in Univariable, Multivariable, and Risk Factor-Adjusted Logistic Regression Analyses of PMI

Polymorphism		Inheritance Mode	Univariable*		Multivariable†		Multivariable, Risk Factor-Adjusted‡		FDR§
			OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]	*P*	
IL6	−572G > C	Additive	2.8 [1.27–5.83]	0.0077	2.75 [1.2–6.3]¶	0.017	2.47 [1.02–5.97]e	0.045	+
ICAM1	1462A > G	Additive	1.9 [1.25–2.91]	0.003	1.82 [1.17–2.85]¶	0.009	1.88 [1.17–3.04]¶	0.009	+
SELE	98G > T	Dominant	0.17 [0.03–0.57]	0.0157	0.19 [0.05–0.81]¶	0.025	0.16 [0.03–0.74]¶	0.019	+
CRP	1846 C > T	Dominant	1.89 [1.01–3.7[	0.0519	2.50 [1.27–5.24]‖	0.011	2.25 [1.11–4.85]‖	0.03	−
LBP	19983T > C	Dominant	2.28 [1.22–4.21]	0.0089	2.37 [1.23–4.53]‖	0.009	2.81 [1.41–5.65]‖	0.003	−
CAT	−844C > T	Additive	0.67 [0.42–1.04]	0.0830	0.57 [0.37–0.93]‖	0.031	0.55 [0.31–0.93]‖	0.03	−
IL1B	−511T > C	Additive	1.59 [0.93–2.75]	0.0948					
	5887C > T	Dominant	0.56 [0.28–1.07]	0.0898					
IL6	−597G > A	Additive	0.62 [0.37–1.01]	0.0602					
CD14	−260C > T	Dominant	0.56 [0.3–1.08]	0.0754					
SELE	561A > C	Dominant	0.10 [0.01–0.46]	0.0231					

*Univariable and †multivariable logistic regression tests for allelic association.

‡Multivariable logistic regression adjusted for duration of aortic cross-clamping, number of coronary grafts and redo-surgery.

§False discovery rate controlled at 10% to adjust for multiple comparisons in univariate tests among 48 polymorphisms.

¶Primary multi-locus genetic model.

‖Alternate multi-locus genetic model.

TABLE 5

Genotype Frequencies for the 6 Polymorphisms Selected in Multivariable Logistic Regression Models

Polymorphism		PMI	No PMI
IL6 −572G > C (rs1800796)	GG	0.784	0.911
	GC	0.216	0.089
ICAM1 1462A > G (rs5498)	AA	0.235	0.405
	AG	0.490	0.464
	GG	0.275	0.131
SELE 98G > T (rs1805193)	GG	0.959	0.799
	GT	0.020	0.184
	TT	0.020	0.017
CRP 1846C > T (rs1205)	CC	0.306	0.455
	CT	0.633	0.467
	TT	0.061	0.078
LBP 19983T > C (rs2232582)	TT	0.542	0.729
	CT	0.417	0.239
	CC	0.042	0.032
CAT −844T > C (rs769214)	TT	0.558	0.437
	CT	0.365	0.429
	CC	0.077	0.134