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Platelet Pl^{A2} Polymorphism and Platelet Activation Are Associated with Increased Troponin I Release after Cardiopulmonary Bypass

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Background: **The Pl^{A2} polymorphism of platelet glycoprotein IIIa has been identified as a prothrombotic risk factor in a number of cardiovascular settings. The aim of this study was to determine whether the Pl^{A2} polymorphism of platelet glycoprotein IIIa and degree of platelet activation were associated with more severe myocardial injury as indicated by troponin I release following cardiopulmonary bypass.**

Methods: **The Pl^{A} genotype was determined in 66 patients undergoing elective coronary artery bypass grafting requiring cardiopulmonary bypass. Troponin I concentrations and the percentage of circulating, activated (CD62P+) platelets were measured at predetermined intervals perioperatively.**

Results: **Forty-six patients were $Pl^{A1,A1}$, and 20 were $Pl^{A1,A2}$ or $Pl^{A2,A2}$. Patients with at least one Pl^{A2} allele had significantly greater postoperative troponin I concentrations than Pl^{A1} homozygotes ($P = 0.006$, analysis of variance). Peak troponin I concentrations also correlated significantly with the increase in circulating, activated platelets ($P = 0.02$, Spearman rank correlation).**

Conclusions: **The Pl^{A2} allele of platelet glycoprotein IIIa is associated with higher troponin I concentrations following cardiopulmonary bypass surgery, suggesting that this platelet polymorphism contributes to perioperative myocardial injury.**

ENHANCED platelet activation and prococagulant activity may contribute to the pathophysiology of arterial vascular events. Pl^{A2}, a polymorphism of the glycoprotein IIIa constituent of the platelet integrin receptor glycoprotein IIb/IIIa, has been proposed as a risk factor for myocardial infarction.[1] Although still somewhat controversial,[2] studies of allelic frequencies in patients with coronary artery disease with and without coronary thrombosis suggest that the Pl^{A2} polymorphism may predispose to increased thrombogenicity.[3,4] Zotz *et al.*[5] studied patients after coronary artery bypass grafting (CABG) surgery, beginning 30 days after surgery and extending to 1 yr, and demonstrated that the Pl^{A2} polymorphism increases the risk of cardiac events and death over this period. We hypothesized that procoagulant alterations in platelet function produced by the Pl^{A2} polymorphism would also exacerbate the degree of myocardial injury that is directly and acutely associated with CABG surgery. This pilot study examined whether the Pl^{A2} polymorphism is associated with increased myocardial injury as indicated by higher postoperative concentrations of the cardiac-specific protein, troponin I (cTpnI). In addition, since enhanced platelet activation is one proposed mechanism for Pl^{A2}-associated vascular injury,[6] the percentage of circulating CD62P+ platelets was also measured perioperatively to determine whether the platelet activation response to cardiopulmonary bypass (CPB) correlated with Pl^{A} genotype or postoperative cTpnI concentrations.

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Material and Methods

Patient Selection and Conduct of Cardiopulmonary Bypass

Power analysis suggested that at least 17 Pl^{A2+} and 17 $Pl^{A1/A1}$ patients would need to be studied to detect a significant cTpnI difference of 5 ng/ml. Given a Pl^{A2} allelic frequency of 28–30%, a minimum of 60 patients was required. After we obtained Human Investigation Committee approval and informed consent, 66 consecutive nonpregnant adults undergoing elective CABG at Yale–New Haven Hospital who were enrolled in the Multicenter Study of Perioperative Ischemia Research Group's prospective study of post-CPB outcomes were studied. All patients underwent CPB using a standardized membrane oxygenator, roller pump, and cardiotomy suction setup.[7]

Determination of Pl^{A} Genotypes

Blood drawn preoperatively into 5 mM EDTA was spotted onto sterile filter paper and dried.[8] Disks cut out of the blood spot were placed in polymerase chain reaction tubes with 20 μl methanol. After drying overnight, two separate polymerase chain reactions were performed for Pl^{A1} and Pl^{A2}, as reported by Skogen *et al.*[9] Amplification products were electrophoresed onto a 2:1 Nusieve:Seakem agarose (FMC Bioproducts, Rockland, ME) gel in TBE buffer. Primers for β-actin were included as a control.[10]

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Table 1. Baseline Patient Demographics

	$PI^{A1,A2}$ and $PI^{A2,A2}$ (n = 20)	$PI^{A1,A1}$ (n = 46)	*P* Value
Mean age (yr)	64.0 ± 10.8 (SD)	69 ± 10.2	0.11
Women (%)	25	17	0.51
Hypertension (%)	75	65	0.57
Diabetes mellitus (%)	35	33	0.99
Previous myocardial infarction (%)	60	50	0.59
Grafts (No.)	3.2 ± 0.8	3.3 ± 0.8	0.83
Bypass time (min)	96 ± 24	100 ± 37	0.89
Cross-clamp time (min)	62 ± 23	65 ± 19	0.30

Platelet Activation

Five blood samples were drawn into fixative (1% paraformaldehyde final concentration) at the start of surgery, prior to and following aortic cross-clamp release, on arrival in the intensive care unit, and in the morning of postoperative day 1. Platelet activation was examined by flow cytometry as previously reported[11] using monoclonal antibodies to CD41 to identify platelets and CD62P to assess their activation status.

Troponin I

Serial blood samples were drawn at the following time points: (1) start of surgery, (2) on arrival in the intensive care unit, (3) 6 h after termination of CPB, and (4) in the morning of postoperative day 1. Samples were centrifuged immediately, and serum aliquots were stored at −70°C. cTpnI concentrations were determined on the Axsym® (Abbott, Abbott Park, IL) EIA system according to the manufacturer's instructions.[12]

Electrocardiograms

Twelve-lead electrocardiograms were obtained preoperatively, on admission to the intensive care unit, between postoperative days 2 and 4, and in addition as clinically appropriate. All electrocardiograms were read and agreed on by two cardiologists blinded to the patient's clinical course and cardiac enzyme concentrations. Cardiac events occurring by electrocardiogram criteria were classified according to Greenson *et al.*[13] as one of the following: (1) persistent new Q waves (at least one third the QRS height) occurring in at least two leads, (2) persistent ST segment changes greater than 0.2 mV in two or more leads, and (3) new-onset bundle branch block.

Statistical Analysis

Genotype was categorized by the presence or absence of the PI^{A2} allele as in previous studies.[1,3] Troponin concentrations for individual time points were normally distributed, and PI^{A1} homozygotes were accordingly compared with PI^{A2} heterozygotes–homozygotes by two-way analysis of variance for troponin concentrations and time. Peak troponin concentrations did not meet the criteria for normality and were therefore analyzed using the nonparametric Mann–Whitney U test. The two genotypes were also compared for preoperative demographic characteristics[14] and intraoperative events by nonparametric tests as follows: (1) for categorical variables (previous myocardial infarction, occurrence of perioperative electrocardiogram changes), the populations were compared using the Fisher exact test, and (2) for continuous variables (age, duration of bypass), the Mann–Whitney U test was used. Correlations between two continuous variables were made using the Spearman rank test. All statistical analysis was performed using Graphpad Prism® software (San Diego, CA).

Results

Clinical Characteristics

Patients were largely white (93%), and the PI^{A} genotype distribution—46 patients (70%) $PI^{A1,A1}$, 16 patients (24%) $PI^{A1,A2}$, and 4 patients (6%) $PI^{A2,A2}$—was similar to those in previously reported studies.[15] Clinical characteristics relevant to risk of perioperative myocardial injury were comparable between PI^{A1} homozygotes *versus* $PI^{A1,A2}$ and $PI^{A2,A2}$ patients (table 1). No patients received long-acting antiplatelet drugs, *i.e.*, GPIIb/IIIa antagonists, with the exception of aspirin within 1 week of elective surgery. All other platelet-active agents were stopped at least 24 h prior to surgery.

Troponin concentrations and PI^{A2} Studies

Figure 1 shows the cTpnI concentrations at each time point with patients stratified by PI^{A} genotype; patients carrying at least one PI^{A2} allele had significantly greater cTpnI concentrations than PI^{A1} homozygotes by analysis of variance ($P = 0.0005$). The four PL^{A2} homozygotes were not outliers and were therefore included with PI^{A2} heterozygotes for all statistical analysis, as has been done in previous studies.[1,3] One $PI^{A1,A2}$ patient had postoperative cTpnI concentrations that met the criteria for outliers by the Grubb method.[16] Assay verification and this patient's clinical course suggested that these values were real, albeit extreme. When this patient's values were modified (divided by SD of the population),[16] PI^{A2} het-

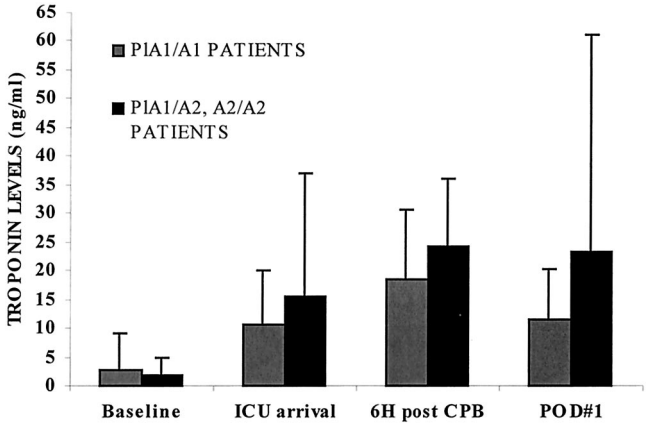

Fig. 1. Troponin I concentrations during and after cardiopulmonary bypass (CPB) according to PL^A genotype. The mean ± SD concentrations of troponin I (cTpnI) are shown in samples drawn preoperatively (baseline), on arrival in the intensive care unit (ICU arrival), 6 h after CPB (6H post CPB), and on the first postoperative day (POD#1), with the $Pl^{A1/A2}$ outlier modified as described in Results. For each time point, $Pl^{A1,A1}$ patients are represented by the striped bars, and $Pl^{A1,A2}/Pl^{A2,A2}$ by solid bars ($P = 0.006$ by analysis of variance).

erozygotes–homozygotes were still significantly higher than Pl^{A1} homozygotes by analysis of variance ($P = 0.006$). Peak cTpnI concentrations were compared in patients with the Pl^{A2} polymorphism *versus* Pl^{A1} homozygotes using the Mann–Whitney test, and Pl^{A2} heterozygotes–homozygotes were significantly higher by this nonparametric test ($P = 0.018$). The peak cTpnIs for all patients are divided into four quartiles in figure 2, and each quartile is stratified by Pl^A genotype. Pl^{A2+} patients represented only 20% and 12% of the first and second

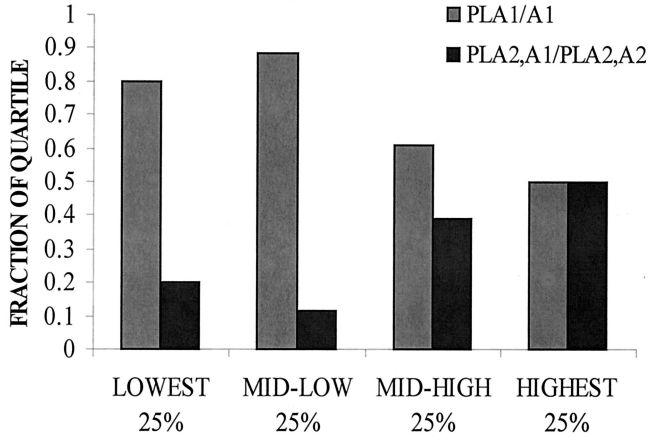

Fig. 2. Association of Pl^A genotypes with peak troponin I cocentrations. Patients were divided into quartiles by peak concentrations of troponin I (cTpnI). The 25% (n = 15) with the lowest peak cTpnI had peak cTpnI 13 or less, the peak cTpnI of the mid-lowest 25% (n = 17) ranged from 14 to 18, the peak cTpnI of the mid-highest (n = 18) ranged from 19–30, and the highest (n = 16) had peak cTpnI greater than 30. For each quartile, the percentage that were $Pl^{A1,A1}$ are represented by the striped bars, and the percentage $Pl^{A1,A2}/Pl^{A2,A2}$ by solid bars. The Pl^{A2} allele was associated with a relative risk of 2.5 times that of the Pl^{A1} homozygotes for having peak postoperative cTpnI in the highest 50th percentile ($P = 0.02$, Fisher exact test).

quartiles containing the lowest cTpnI concentrations, respectively; by contrast, Pl^{A2+} patients made up 39% and 50% of the third and fourth quartiles containing the highest cTpnI concentrations, respectively. A Fisher exact test was used to compare the proportion of each genotype in the 50% of patients with the lowest *versus* the highest troponins. The Pl^{A2} allele conferred a relative risk of 2.3 for having peak postoperative cTpnI concentrations in the highest 50th percentile (95% confidence interval, 1.06–5.2; $P = 0.02$). Evaluation of the individual time points (Mann–Whitney U test) revealed that the 6-h post-CPB time point differed significantly between the Pl^A genotypes ($P = 0.02$), but the difference on postoperative day 1 did not reach the level of statistical significance ($P = 0.11$).

Platelet Activation

The percentage of circulating activated platelets in all patients increased over the course of CPB, as previously detailed.[11] Peak platelet activation correlated significantly with peak cTpnI concentrations by the Spearman rank test ($P = 0.024$). However, the two Pl^A allelic groups did not differ significantly with respect to peak platelet activation ($P = 0.37$ by Mann–Whitney test).

Electrocardiogram Analysis

With respect to postoperative electrocardiogram changes, one patient ($Pl^{A1,A1}$) had a baseline left bundle branch block that obviated postoperative electrocardiogram interpretation. Of the 65 patients with assessable electrocardiograms, 12 demonstrated electrocardiogram evidence of a new post-CPB cardiac event; one new Q-wave ($Pl^{A1,A1}$), two new rhythm disturbances (one $Pl^{A1,A1}$ and one Pl^{A2+}, each with new bundle branch block), and the remaining 9 (6 $Pl^{A1,A1}$and 3 Pl^{A2+}) showed persistent ST segment changes. A total of 8 of the 45 Pl^{A1} homozygotes (15%) and 4 of the 20 Pl^{A2+} patients (20%) had electrocardiogram evidence of a cardiac event; this difference was not statistically significant by Fisher exact test ($P = 0.99$).

Discussion

This pilot study has demonstrated in a modest number of patients undergoing CABG that the presence of the Pl^{A2} allele is associated with higher cTpnI concentrations following CPB as compared with Pl^{A1} homozygotes. We found that the peak increase in perioperative platelet activation correlated significantly with peak cTpnI concentrations. However, patients who were heterozygous–homozygous for the Pl^{A2} allele did not differ significantly from Pl^{A1} homozygotes with respect to this single marker of platelet activation (α-granule release-specific). Studies have suggested that the Pl^{A2} allele confers an increased risk for vascular occlusive events, but

the mechanism responsible for this platelet hypercoagulability remains controversial.[1–4]

Weiss *et al.*[1] demonstrated a greater prevalence of the PI^{A2} allele in coronary thrombosis patients, and other studies[3,17] have supported this finding. Glycoprotein IIIa is the β_3-subunit common to the platelet fibrinogen receptor glycoprotein IIb/IIIa ($\alpha_{IIb\beta3}$ integrin) and the platelet–endothelial vitronectin receptor ($\alpha_{v\beta3}$ integrin). The PI^{A2} polymorphism results from a $Leu^{33} \rightarrow Pro$ substitution in the glycoprotein IIIa amino terminus.[18] The association of the PI^{A2} allele with coronary artery disease has been controversial. Some studies[17] have found a greater degree of coronary stenosis in PI^{A2+} patients, but a number of other studies have not confirmed this polymorphism as a risk factor for atherosclerosis.[2,19,20] Instead of predisposing to greater atherosclerotic disease, other investigations have found that the PI^{A2} allele increases the risk of thrombosis in established atherosclerotic coronary arteries.[3,4,21] Zotz *et al.*[5] have demonstrated that the PI^{A2} polymorphism increases the chance of cardiac events or death in the period 2–12 months after CABG surgery. We have now demonstrated that this platelet polymorphism increases the risk of myocardial injury that is directly and temporally associated with the operative procedure itself.

The precise mechanistic link between the PI^{A2} polymorphism and increased risk of thrombosis is still unclear. Our study suggests that heightened platelet activation is associated with greater myocardial injury perioperatively in the CABG patient. However, although peak increases in platelet activation in all patients correlated with peak cTpnI concentrations, those patients carrying the PI^{A2} allele did not demonstrate significantly greater platelet activation increases than did PI^{A1} homozygotes. Analogous to our findings, Carter *et al.*[15] found that while both the PI^{A2} allele and platelet activation markers (in their case, platelet factor 4 and β-thromboglobulin) were independently correlated with the occurrence of stroke and poststroke mortality, PI^{A2+} stroke patients did not demonstrate higher concentrations of platelet activation markers than PI^{A1} homozygotes. Meiklejohn *et al.*[22] similarly did not find a greater percent CD62P+ platelets in PI^{A2+} patients with stroke, although stroke patients as a whole showed a greater circulating percent CD62P+ platelets than in healthy controls.

Some *in vitro* studies of PI^{A2+} homozygous individuals have demonstrated increased platelet aggregability,[23,24] increased fibrinogen binding,[25] and enhanced platelet adhesion and clot retraction[26] in PI^{A2+} platelets. These alterations could account for the allele's arterial prothrombotic effects and, by creating a more robust platelet plug, would not necessarily increase the percentage of circulating CD62P+ platelets. The only *in vitro* study to show a difference in CD62P expression according to PI^{A} genotype was the study by Michelson *et al.*,[6] which found a lower threshold for platelet activation and CD62P expression only in patients homozygous for the PI^{A2} allele. In the current study, only four patients were PI^{A2} homozygotes, too few to credibly examine the relation between PI^{A2} homozygosity and the platelet CD62P response to CPB. It is possible that heterozygosity or homozygosity for the PI^{A2} allele and CPB-induced increases in circulating activated platelets represent independent pathophysiologies enhancing platelet function by different pathways, each uniquely contributing to the myocardial injury associated with CPB. Alternatively, the relation between the PI^{A2} allele and platelet activation may be too complex to demonstrate in a study of this size.

Assessing the extent of myocardial injury in the post-CPB patient is difficult.[27–29] Perioperative myocardial infarction diagnosed by electrocardiogram criteria is clearly associated with a poor long-term outcome.[30] However, new Q waves are not particularly sensitive markers of myocardial infarction[31]; indeed, most myocardial infarctions associated with non-CPB surgery do not result in Q waves.[32] Technetium-99 m pyrophosphate scans revealed a 21% incidence of acute myocardial infarction in a population of post-CPB patients with only a 3% incidence of new Q waves.[33] Given these limitations, many investigators have turned to myocardial-specific enzyme leakage, and cTpnI in particular, as a more reliable marker of cardiac injury in the peri-CPB patient.[34] One problem impeding application of cTpnI measurements is the difficulty defining the range of "normal" for the post-CPB patients. This task is hampered by the disparity between commercial cTpnI assays. The three most widely used commercial cTpnI assays report upper limits of normal (defined in non-CPB patients) that span a 20-fold range. A recent study of perioperative myocardial injury in CPB patients found that samples tested with two different assays differed by a factor of 20,[35] underscoring the difficulties faced when attempting to establish widely applicable standards for post-CPB myocardial injury. We chose not to attempt to define a cTpnI threshold for myocardial infarction in our patients, but instead analyzed peak cTpnI concentrations as a continuous variable using nonparametric statistics.[14,36]

The risks associated with elevated cTpnI concentrations after CPB have not been clearly established, but in the acute coronary care setting, even modest cTpnI elevations have predictive value for complications attributable to myocardial injury.[37] Indeed, a recent study of post-CPB myocardial injury found that the degree of CK-MB elevation independently predicted adverse outcome.[38] The current study's finding that cTpnI concentrations correlate with both a genetic variant predisposing to enhanced *in vitro* platelet function and the increase in circulating activated platelets suggests that heightened platelet function in the peri-CPB patient imposes myocardial risk.

One limitation of this study is the timing of samples for cTpnI determination, which were drawn in the early post-CPB period. Some investigators[13,39,40] have demon-

strated delayed cTpnI leakage after CPB, peaking as late as 48 h postoperatively, well after the last sample taken in the current study (18–24 h after CPB). By contrast, other investigators[14,35,36,41] have demonstrated peak post-CPB cTpnI concentrations in the first postoperative day, which would have been captured in the current study. Thus, it is possible that some $Pl^{A1/A1}$ patients might have developed late (48-h) cTpnI increases, but we know of no specific rationale for why that might occur more frequently than in Pl^{A2+} subjects.

In summary, this pilot study has demonstrated a significant link between the Pl^{A2} allele and the concentrations of cTpnI associated with CPB, suggesting that the Pl^{A2} polymorphism may be a risk factor for greater perioperative myocardial injury. In addition, the peak increase in platelet activation correlated with peak cTpnI concentrations, independent of Pl^{A} genotype. Larger studies will be needed to confirm these findings and to further explore the role of platelet procoagulant function in the myocardial injury associated with CPB.

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