

SCA 10

FACTOR VII LEVELS DURING CARDIOPULMONARY BYPASS CORRELATE WITH FACTOR VII GENOTYPES AND THROMBIN GENERATION

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Introduction: Coagulation system activation is a pivotal event mediating post-cardiopulmonary bypass (CPB) morbidity (1, 2). However, the genetic variables that regulate the involvement of the extrinsic pathway (3-5) have not been explored. Here, we present evidence for the factor VII R353Q polymorphism in regulation of factor VII antigen (FVII:Ag) levels during CPB, and show that baseline FVII:Ag correlates with thrombin generation following CPB.

Methods: We measured plasma factor VII antigen (FVII:Ag) and prothrombin fragment F1.2 levels from 57 patients undergoing CPB. Patients were enrolled according to IRB-approved guidelines. Plasma was isolated from blood drawn at the beginning of surgery (Baseline), 10 minutes after initiation of CPB (On CPB), one hour after initiation of CPB (CPB 1 Hr), 10 minutes after protamine administration (Off CPB), and 24 hours after ICU arrival (Next Day). Plasma FVII:Ag and F1.2 levels were determined by commercial ELISA methods. DNA was isolated from blood drawn at the beginning of surgery, and FVII 353R/Q genotype was determined using the method of Heywood and colleagues (6). Statistical analysis consisted of independent t-test, ANOVA for repeated measures, and Spearman's correlation.

Results: The frequency of the 353Q allele in the study population was 8.9% and the population was in Hardy-Weinberg Equilibrium. As shown in Figure 1, FVII:Ag levels differed at baseline between FVII RR homozygotes and subjects carrying at least one FVII Q allele. The FVII R353Q polymorphism had a significant impact on FVII:Ag levels ($p < 0.002$), with FVII:Ag levels 23-35% lower in subjects carrying at least one 353Q allele for the entire perioperative period. Prothrombin F1.2 level, while appearing higher for subjects with FVII 353RR genotype, was not significantly dependent on this genotype ($p = 0.526$; Figure 2). However, thrombin generation during CPB, as evidenced by prothrombin F1.2 fragment levels immediately following CPB, was found to be significantly correlated with baseline FVII:Ag levels (Spearman's correlation $r = 0.311$; $p = 0.005$) as shown in Figure 3.

Discussion: Factor VII plasma levels are strongly influenced by genotype. Here, FVII:Ag levels between FVII RR and FVII RQ+QQ patient groups were essentially parallel during CPB, with significantly lower levels observed in subjects carrying at least one 353Q allele. Coagulation system activation correlated significantly with baseline FVII:Ag levels, suggesting involvement of the tissue factor pathway in thrombin generation during CPB. Larger studies with inclusion of confounding variables are needed to address whether FVII genotype is directly associated with thrombin generation during CPB. These studies reflect our growing understanding of the role specific genetic variants may play in the assessment of perioperative risk.

References:

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