Risk Factors for Activated Protein C Resistance in Patients with Congenital Heart Disease

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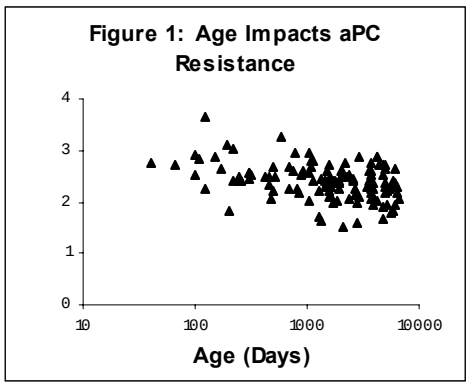
Introduction: Children with congenital heart disease often have multiple defects in hemostasis (*1, 2*), and are subject to interventions such as cardiopulmonary bypass, which invoke physiologic derangements unique to the pediatric population (*3-5*). Resistance to aPC represents a procoagulant phenotype with multiple contributing factors, which include age, factor VIII:C levels, inflammation, and several known factor V mutations (*6*). Because response to aPC may be an important factor in determining outcome following cardiac surgery (*7, 8*), we examined contributing factors for aPC resistance in our pediatric cardiac surgery population.

Methods: Following IRB approval and informed consent from parents, we enrolled 124 children with congenital heart disease, undergoing catheterization procedures. Blood was drawn at the time of catheterization for plasma storage. Resistance to aPC was measured by a clot-based assay (DiaPharma). Clinical parameters consisted of age; use of aspirin, coumadin, and digoxin; history of thrombosis, and room air saturations. These data were recorded from chart review. Data analysis consisted of nonparametric bivariate correlation (Spearman's rho), and multivariate linear regression.

Results: Room air saturation and patient age were both associated with aPC resistance, indicated by decreased aPC ratio (Figures 1 and 2; $p<0.001$). Digoxin use, a marker for impaired ventricular function, was associated with sensitivity to aPC ($p=0.003$). Unlike findings in adults, neither coumadin use nor history of thrombosis was associated with decreased aPC ratio. Using a stepwise multivariate regression analysis, we again observed that room air saturation and patient age were associated with resistance to aPC, and together explained about 17.5% of the variability in aPC ratio (Table 1).



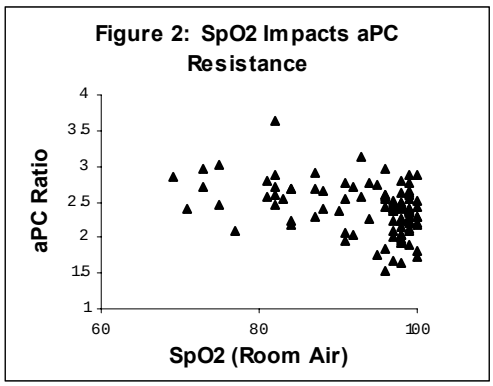


Table 1: Linear Regression Model for aPC Ratio			
Parameter	*B Coeff*	*Std Err*	*P*
Age (Years)	-0.0143	0.0066	0.032
SpO2	-0.0144	0.0043	0.001
Y-intercept	3.83	0.387	<0.001

Conclusions: Resistance to aPC in this population is influenced by an array of factors not observed in adults. Patients with lower aPC ratios tended to be older and noncyanotic. How these factors contribute to aPC resistance, and the impact of additional genetic and environmental factors is the subject of an ongoing investigation. In addition, how aPC resistance impacts the response of these patients to extracorporeal circulation is also being investigated.

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