Congenital Cardiac Lesions Involving Systolic Flow Abnormalities Are Associated With Platelet Dysfunction in Children

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Background. **Shear stress-induced platelet dysfunction (PD) is prevalent among adults with aortic stenosis. Our aim was to determine whether abnormal platelet function was associated with specific congenital cardiac lesions in children.**

Methods. **The charts of 407 children who had undergone cardiopulmonary bypass and had preoperative platelet function analysis were evaluated. Patients were assigned to 1 of 11 different lesion categories. Platelet dysfunction (PD) was defined as prolonged closure time (CT) as measured with a platelet function analyzer. Odds ratio (OR) estimates for prolonged CT were calculated for each lesion category. Mean CTs were compared with Tukey-Kramer separated means testing. Analysis of variance modeling was used to determine association between hematocrit value and CT.**

Results. **CT in patients with ventricular septal defects (VSD) and right ventricular outflow tract obstruction (RVOTO) lesions was prolonged. OR analysis found that patients with VSDs (OR, 2.46) or RVOTO (OR, 2.88) had at least a 95% probability of an abnormal CT. In contrast, patients with atrial septal defect (ASD), bidirectional Glenn procedure (BDG), and pulmonary insufficiency (PI) had a reduced probability of a prolonged CT ($p < 0.05$). A similar pattern was seen in parametric analysis comparing mean CTs across lesion categories. A lower preoperative hematocrit value was associated with prolonged CTs across all lesion types ($p < 0.05$).**

Conclusions. **PD was common in children with congenital cardiac lesions involving systolic flow abnormalities and was uncommon among children with lesions having diastolic abnormalities. Lower preoperative hematocrit values were associated with prolonged CTs, suggesting subclinical bleeding secondary to excessive platelet shearing.**

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Blood exerts a force as it passes over the endothelium. This is known as fluid shear stress and is generated by loss of velocity in blood flow at the interface between the blood and the vessel wall. The magnitude of any fluid shear stress is determined by the velocity and the viscous properties of the fluid and the roughness and diameter of the tube in which the fluid is flowing. Fluid shear stress is increased as blood passes through a stenosis or an intracardiac shunt.

In adults, platelet dysfunction (PD) related to fluid shear stress was first described in 1975 [1]. Fluid shear stress in the circulation can be associated with reversible PD in hemodynamic lesions, notably aortic stenosis [2, 3]. PD associated with aortic stenosis is a risk factor for bleeding [4], which is something that had been observed in these patients as far back as the 1950s [5].

Platelet function analysis (PFA) (PFA-100; Dade-Behring Inc, Miami, FL) is an in vitro assay that evaluates platelet function. It is a reliable and sensitive screening tool for detecting PD in patients with acquired von Willebrand disease resulting from high shear stress [6–8]. In the setting of high fluid shear across a stenotic aortic valve, acquired von Willebrand disease develops secondary to preferential cleavage of the largest von Willebrand factor (vWF) multimers [9]. In adults with aortic valvular stenosis, PFA-100 results are useful clinically because they are predictive of perioperative transfusion requirements and can help identify which patients may benefit from platelet transfusions [10, 11].

Children with congenital cardiac defects have abnormal fluid shear across stenotic valves as well as through complex septal defects, long-segment synthetic grafts, and calcified conduits. Although PFA-100 values for healthy children have been described [12], our understanding is very limited in the context of congenital heart disease. Two small case series of patients with congenital cardiac defects and acquired von Willebrand syndrome have been described. Gill and colleagues [13]

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Abbreviations and Acronyms

BDG = bidirectional Glenn procedure
BTS = (modified) Blalock-Taussig Shunt
cADP = collagen adenosine diphosphate
cASD = complex atrial septal defect
cEPI = collagen epinephrine
CT = closure time
cVSD = complex ventricular septal defect
LVOTO = left ventricular outflow tract obstruction
PD = platelet dysfunction
PFA-100 = Platelet Function Analyzer-100
PI = pulmonary insufficiency
RVOTO = right ventricular outflow tract obstruction
sASD = simple atrial septal defect
sVSD = simple ventricular septal defect
TOF = tetralogy of Fallot
VSD = ventricular septal defect

did not perform any PFA-100 testing and Onimoe and coworkers [14] included PFA-100 testing results in only 11 patients and noted that all had an abnormal closure time (CT).

The aim of the current study was to describe the prevalence of PD in a large cohort of children with congenital heart disease using PFA-100 testing and to determine whether this dysfunction was differentially associated with specific types of cardiac lesions.

Patients and Methods

The charts of 639 consecutive patients between the ages of 30 days and 18 years undergoing elective cardiac operations with the use of cardiopulmonary bypass between 2006 and 2010 at Oregon Health & Science University were analyzed. Neonates were excluded because of known differences in PFA-100 results compared with older children [15]. Laboratory analysis included preoperative complete blood count, activated prothrombin time, international normalized ratio, complete metabolic panel, liver function testing, and PFA-100 CTs. Inclusion criteria also comprised a hematocrit value greater than 28% and a platelet count greater than 100×10^9/L, because values less than these levels lead to the prolongation of PFA-100 CTs [16]. Because of the known association between PD and renal and liver disease, age-appropriate urea, creatinine, and transaminase levels were also required for inclusion [17]. Any patient who had not undergone PFA-100 testing or whose preoperative laboratory testing was incomplete or with a specimen collection date longer than 30 days before operation was excluded. The reason patients who did not have PFA-100 testing done was an insufficient blood sample. These patients were not different from the patients who had PFA-100 testing performed. Mean collection time ($\pm$ 1 standard deviation) was 2.2 $\pm$ 0.2 days before operation. Patients with bleeding diatheses as well as those who had taken aspirin or nonsteroidal antiinflammatory medication within 7 days of blood sampling were also excluded.

Patients who fulfilled the preceding criteria were then grouped into 1 of 11 cardiac lesion categories based on preoperative echocardiography, the results of which were confirmed by review of the operative report. Patients who had cardiac anatomy that did not fulfill any lesion category included patients with an anomalous coronary artery, an intracardiac tumor, or a pulmonary artery aneurysm; these patients were also excluded. Fifteen patients underwent 2 separate surgical procedures a minimum of 6 months apart. For the purpose of this study, they were considered different cases because each had a different diagnosis before operation and thus had an independent impact on platelet function. Excluded patients were analyzed only for age, sex, or lesion category selection bias. Patients were grouped into 3 age categories (30 days to 1 year, 1 year to <9 years, and 9–18 years) based on age-related maturation of the hemostatic system [18]. The local institutional review board approved this study.

Cardiac Lesion Classification

Complete 2-dimensional, pulse-wave Doppler, color-Doppler flow mapping, and M-mode echocardiograms (Sonos 7500 or iE33; Philips Medical Systems, Andover, MA) were obtained in all patients. Cardiac lesion categories were based on anatomic and physiologic considerations that we believed may impact shear as follows: (1) simple atrial septal defect (sASD), (2) bidirectional Glenn procedure (BDG), (3) pulmonary insufficiency (PI), (4) complex atrial septal defect (cASD), (5) complete atrioventricular septal defect (cASD), (6) modified Blalock-Taussig shunt (BTS), (7) tetralogy of Fallot (TOF) with outflow tract obstruction, (8) left ventricular outflow tract obstruction (LVOTO), (9) simple ventricular septal defect (sVSD), (10) right ventricular outflow tract obstruction (RVOTO), and (11) complex ventricular septal defect (cVSD).

The cASD category included patients with an ASD in association with either anomalous pulmonary venous return or a cleft in the left atrioventricular valve. The LVOTO category also included patients with mitral stenosis, aortic valve stenosis, aortic coarctation, or arch hypoplasia in isolation or in any combination. The cVSD group included those eligible for a 2-ventricle repair with an additional shearing defect such as subaortic stenosis or coarctation of the aorta.

Platelet Function Analyzer

The PFA-100 system provides a quantitative, rapid, and simple in vitro method of assessing primary platelet-related hemostasis. It simulates high-shear platelet function within disposable test cartridges. Citrated whole blood is aspirated at a shear rate of 5000 to 6000 per second through a 150-μm aperture cut into a collagen-coated membrane impregnated with either epinephrine or adenosine diphosphate (ADP). Epinephrine and ADP act as platelet agonists and cause platelet adherence and