# High Flow Velocity Through Congenital Cardiac Lesions Predicts Preoperative Platelet Dysfunction

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*Background.* **Platelet dysfunction resulting from abnormal fluid shear stress has been reported in adults with aortic stenosis. Blood flowing through a congenital heart defect at greater than normal velocity is subjected to increased shear stress. The primary aim was to determine whether peak flow velocity through congenital cardiac lesions predicts preoperative platelet dysfunction.**

*Methods.* **The charts of 402 patients who underwent cardiopulmonary bypass and had preoperative platelet function analysis were evaluated. Platelet dysfunction was measured as a prolonged closure time (CT) in seconds with a platelet function analyzer. Echocardiography was used to determine peak velocity. The relationship between peak velocity and CT was analyzed using linear regression and Kaplan-Meier estimation.**

*Results.* **The distribution of peak velocity was bimodal. The mean velocity of the lower group was 1.9 m/second and the higher group was 4.2 m/second. Univariate analysis showed age, weight, peak velocity, hematocrit, and Risk Adjustment for Congenital Heart Surgery score to be associated with prolonged CT. Using multivariable analysis, prolonged CT was significantly associated with peak velocity ($p < 0.001$). For each 1m/second increase in peak velocity the CT increased by over 9 seconds ($p < 0.001$). In addition, a median CT increase of more than 6 seconds was also associated with a 5 percentage point drop in hematocrit ($p = 0.04$).**

*Conclusions.* **Platelet dysfunction is associated with high blood flow velocity through congenital cardiac lesions. Lower preoperative hematocrit was associated with prolonged CT, which may suggest subclinical bleeding secondary to platelet dysfunction.**

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A parabolic velocity profile is generated by blood flow in a straight vessel. This effect results in a minimum velocity and maximal shear at the periphery of the vessel. Platelets in blood vessels flow near the periphery and hence are subjected to the maximal shear stress [1].

Brown and colleagues [2] reported the association between platelet dysfunction and shear stress. Platelet aggregation under conditions of high shear stress depends upon the presence of plasma von Willebrand factor (vWF) and functional platelet receptor complexes GpIb/IX/V and GpIIb-IIIa [3–5]. Platelet dysfunction resulting from abnormal fluid shear stress has been associated with hemodynamic lesions, in particular aortic stenosis [6]. Under conditions of high shear stress there is proteolysis of high molecular weight multimers of vWF by a metalloproteinase, ADAMTS-13 [7]. These high molecular weight multimers are responsible for shear induced platelet aggregation [5].

Platelet function analysis (PFA-100; Dade-Behring Inc, Miami, FL) is an in vitro assay that evaluates platelet function [8]. Only limited information has been available for PFA-100 values in children with congenital cardiac lesions, although PFA-100 values for healthy children have been described [9]. Congenital cardiac lesions involving outflow tract obstruction, stenotic valves, and calcified conduits have been associated with abnormal fluid shear stress. Recently, congenital cardiac lesions involving systolic flow abnormalities have been shown to be associated with abnormal PFA-100 results in contrast to lesions with diastolic flow abnormalities [10]. Blood flowing through a heart defect at greater than normal velocity is subjected to increased shear stress [11]. We aimed to determine the relationship between peak velocity through congenital cardiac lesions and abnormal preoperative platelet function.

## Material and Methods

### *Patients*

With the approval of the Oregon Health & Science University Institutional Review Board, the charts of consecutive patients who had undergone cardiac surgery with the use of cardiopulmonary bypass between 2008 and to the beginning of 2014 were reviewed. Patients who had not undergone PFA-100 testing were excluded, generally because the blood sample was insufficient. Neonates were excluded because healthy neonates have

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shorter closure time (CT) compared with older children [12]. Patients above the age of 18 years were excluded as this study focuses on children. Single ventricle patients were excluded from the study. All patients had their PFA-100 test done within 30 days before surgery. Table 1 categorizes the lesions of our study participants.

### *Preoperative Peripheral Venous Blood Analysis*

THE PLATELET FUNCTION ANALYZER. The PFA-100 system provides a quantitative in vitro method of assessing primary platelet-related hemostasis. It simulates high shear-induced platelet function within disposable test cartridges. Citrated whole blood is aspirated at a shear rate of 5,000 to 6,000/second through a 150 μm aperture cut into a collagen-coated membrane impregnated with either epinephrine (cEPI) or adenosine-5-diphosphate (cADP). Epinephrine and ADP act as platelet agonists and cause platelet adherence and aggregation. The platelet plug that forms occludes the aperture. The time taken for the aperture to occlude is known as the CT and is measured in seconds. The CT provides a measure of overall platelet-related hemostasis. Normal reference ranges for CT within our clinical laboratory are 85 to 148 seconds for a collagen epinephrine (cEPI) cartridge and 64 to 113 seconds for collagen ADP (cADP) cartridge. The cEPI cartridges are more sensitive than cADP cartridges in detecting mild platelet disorders, mild von Willebrand disease (vWD), and medication side effects such as NSAIDS [8].

Blood analysis included preoperative complete blood count, activated partial thromboplastin time, international normalized ratio, urea, serum creatinine, electrolytes, liver function tests and PFA-100® closure times. All these tests were obtained routinely for every patient. Inclusion criteria for further analysis included a hematocrit greater than 28% and a platelet count greater than $10^{11}$ L, because values below these ranges lead to significant prolongation of CT [13].

*Table 1. Frequency Distribution of Lesion Type*

| Category/Type of Lesion | Frequency |
|---|---|
| Right ventricular outflow tract obstruction (n = 113) | |
| Tetralogy of Fallot | 62 |
| Others | 51 |
| Left ventricular outflow tract obstruction (n = 47) | |
| Subvalvular aortic stenosis | 22 |
| Valvular aortic stenosis | 16 |
| Supravalvular aortic stenosis | 9 |
| Valvular insufficiency (n = 32) | |
| Pulmonary insufficiency | 21 |
| Tricuspid regurgitation | 5 |
| Aortic insufficiency | 3 |
| Mitral regurgitation | 3 |
| Ventricular septal defect | 86 |
| Atrioventricular septal defect | 45 |
| Atrial septal defect | 42 |
| Partial anomalous pulmonary venous return | 12 |
| Pulmonary atresia with ventricular septal defect | 6 |
| Coarctation of the aorta | 4 |
| Blalock-Taussig shunt | 2 |
| Congenitally corrected transposition of great arteries | 2 |
| Total anomalous pulmonary venous return | 2 |
| Patent ductus arteriosus | 1 |
| Others | 8 |
| Total | 402 |

### *Peak Velocity Through Congenital Cardiac Lesions*

ECHOCARDIOGRAPH. Doppler echocardiography was used to determine the peak velocity of blood through congenital heart lesions. Complete two-dimensional, pulse-wave Doppler, color-Doppler flow mapping, and M-mode echocardiograms were performed on all patients (iE33; Phillips Medical Systems, Briarcliff Manor, NY). If a patient had multiple cardiac lesions, the lesion having the highest (peak) velocity was chosen. A total of 15 patients did not have their peak velocity measured so they were excluded from the analysis. Echocardiograms were performed by a cardiologist or sonographer and corroborated by a pediatric cardiologist.

### *Statistical Methods*

Continuous variables were explored graphically to note the general distribution of the measurements and then summarized using means and standard deviations or medians and interquartile range; categoric variables were summarized in terms of frequencies and percentages. A mixture of 2 normal (Gaussian) densities was fit to the distribution of peak velocity measurements with parameters for the supporting densities estimated by maximum likelihood. The resulting posterior probabilities from the mixture model were used to classify peak velocity values as either "low" or "high," according to whichever class (low or high) had the highest posterior probability for a given observation [14]. The CT measured by the cADP and cEPI cartridges was recorded as 300 seconds if actual CT was at least that long. Ordinary least squares regression would be affected by these extreme censored observations; consequently, quantile regression was used to estimate the median (ie, 50th percentile) CT as a function of 1 or more explanatory variables and Spearman's rank correlation was used to quantify crude associations involving CT. Lastly, Kaplan-Meier estimates were used to explore CT according to the low and high peak velocity classifications and to estimate the proportion of subjects with CTs at or before the manufacturer's recommended threshold separating normal and abnormal times. Statistical significance was set to 0.05. Stata ver. 13.1 (StataCorp LP, College Station, TX) was used for basic descriptive statistics, quantile regression, and Kaplan-Meier estimation while R (ver. 3.0.2, R Core Team) was used to fit the initial mixture model to peak velocity measurements.

## Results

### *Sample Demographics*

A total of 402 patients were available for analysis. Of these, 362 (90%) had CT recorded using the cADP