The Heart Surgery Forum #2014-461
18 (1), 2015 [Epub February 2015]
doi: 10.1532/hsf.1228

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# Inflammation and Congenital Heart Disease Associated Pulmonary Hypertension

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## ABSTRACT

**Background:** Increased blood flow may trigger pulmonary arterial wall inflammation, which may influence progression of pulmonary artery hypertension in patients with congenital heart disease. In this study, we aimed to investigate the correlation between preoperative inflammation markers and pulmonary arterial hypertension.

**Methods:** A total of 201 patients with pulmonary hypertension were enrolled in this study retrospectively; they had undergone open heart surgery between January 2012 and December 2013. Patients' preoperative C-reactive protein (CRP), neutrophil to lymphocyte ratio, red blood cell distribution width, pulmonary pressures, and postoperative outcomes were evaluated.

**Results:** Patient age, neutrophil to lymphocyte ratio, red blood cell distribution width, and CRP were found to be significantly correlated with both preoperative peak and mean pulmonary artery pressures. These data were entered into a linear logistic regression analysis. Patient age, neutrophil to lymphocyte ratio, and CRP were found to be independently correlated with peak pulmonary pressure ($P < .001$, $P < .001$, and $P = .004$) and mean pulmonary artery pressure ($P < .001$, $P < .001$, and $P = .001$), whereas preoperative mean pulmonary artery pressure was found to be independently correlated with intensive care unit stay ($P < .001$). No parameter was found to be significantly correlated with extubation time and mortality. Eighteen patients had experienced pulmonary hypertensive crisis; in this subgroup, patients' mean pulmonary artery pressure and neutrophil to lymphocyte ratio were found to be significant ($P = .047$, $P = .003$).

**Conclusion:** Preoperative inflammation markers may be correlated with the progression of pulmonary hypertensive disease, but further studies with larger sample size are needed to determine the predictive role of these markers for postoperative outcomes.

*Received November 29, 2014; received in revised form January 9, 2015; accepted February 23, 2015.*

*Thank you to Professor Dr. Nurhan Ince for her contribution to the statistical analysis.*

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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary artery pressure >25 mmHg. It is one of the most influential components of congenital heart disease with left to right shunt, or in some cases with left side lesions leading to postcapillary pulmonary hypertension [Price 2012]. Increased blood flow and pressure cause abnormal shear stress, circumferential wall stretch, and endothelial dysfunction in pulmonary arteries. Overexpression of vasoactive mediators including endothelin-1 and prostacyclin result in vasoconstriction. On the other hand, shear stress and inflammation-induced vascular endothelial and fibroblast growth factors promote thickening of the intima, media and adventitia, proliferation of smooth muscle, and increased intracellular matrix deposition [Adatia 2010].

Increased blood flow related mechanical signals may promote arterial wall inflammation. Leucocyte and platelet activation play a crucial role in vascular response to shear

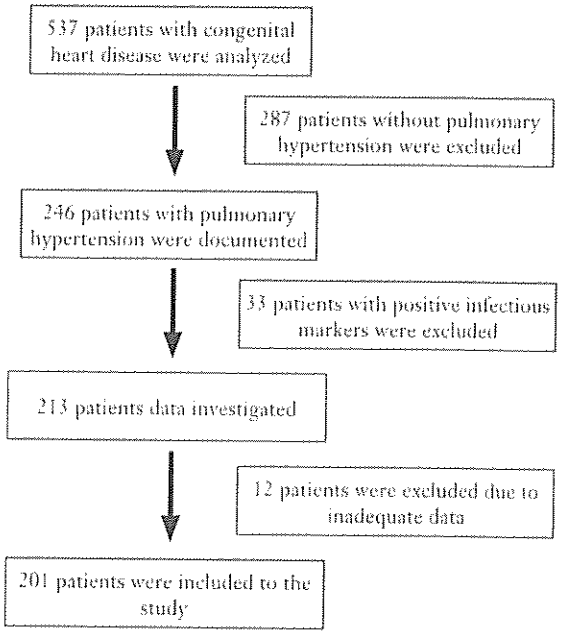


Figure 1. Flow diagram of the study.

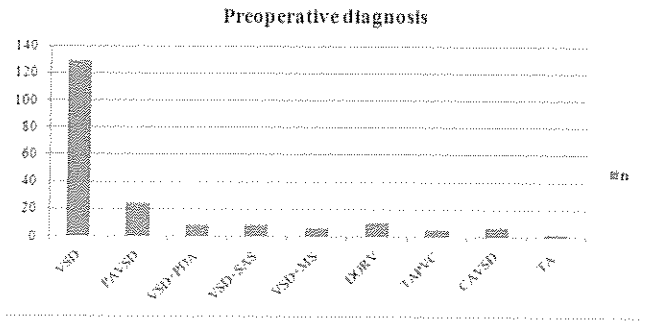


Figure 2. Distribution of patients' diagnoses. VSD indicates ventricular septal defect; PAVSD, partial atrioventricular septal defect; PDA, patent ductus arteriosus; SAS, subaortic stenosis; DORV, double outlet right ventricle; MS, mitral stenosis; TAPVC, total anomalous pulmonary venous connection; CAVSD, complete atrioventricular septal defect; TA, truncus arteriosus.

stress [Iwaki 2009]. Activated neutrophils are strongly associated with various pathophysiologic processes. In the last decade, counts and distribution of leucocyte subtypes have been widely studied in the etiology of numerous diseases [Bhat 2013; Solak 2013; Tamhane 2008].

In the present study, we aimed to investigate correlation of C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), red blood cell distribution width (RDW), and congenital heart disease associated pulmonary hypertension.

## MATERIALS AND METHODS

We retrospectively reviewed 537 patients who underwent open heart surgery between January 2012 and December 2013; 246 patients with pulmonary hypertension were included in our study. Thirty-three patients who had positive preoperative infection markers (patients with leukocytosis, high C-reactive protein (>0.5 mg/dL), or clinical and/or laboratory documented infectious disease) were excluded. Twelve patients were also excluded due to inadequate data. Two hundred and one patients were enrolled in the study (Figure 1). Patients' diagnoses are summarized in Figure 2. Patients' preoperative examination charts, laboratory results, and postoperative intensive care unit files were reviewed. Patient age, sex, diagnosis, preoperative systolic and mean pulmonary artery pressures, preoperative leucocyte counts, neutrophil to lymphocyte ratio, red blood cell distribution width, and C-reactive protein values were investigated. Patients' postoperative systolic and mean pulmonary pressures, intubation times, intensive care unit stay, pulmonary hypertensive crisis, iloprost (analogue of prostacyclin) treatment, and mortality were also documented. Preoperative patient characteristics are summarized in Table 1. Data were analyzed statistically.

### *Operative Management*

All procedures were conducted under volatile anesthesia with sevoflurane (Sevorane Liquid, Abbott Laboratories, USA) and cardiopulmonary bypass with aorto-bicaval cannulation (DLP Medtronic, USA; Terumo Advanced Perfusion System 1 heart lung machine and Capiox RX05 Oxygenator, Terumo Medical Corporation, USA). Antegrade cold crystalloid cardioplegia (Plegisol Hospira, USA) was used for myocardial protection. A dacron patch and bovine pericardium were used for ventricular septal defect closure and right ventricle outflow tract reconstruction.

Table 1. Preoperative Characteristics of Patients*

| | Parameter |
|---|---|
| n | 201 |
| Age, months | 18.28 ± 16.84 |
| Sex, m/f | 133/68 |
| Weight, kg | 8.51 ± 4.08 |
| Preop ppap, mmHg | 71.72 ± 23.40 |
| Preop mpap, mmHg | 47.64 ± 17.10 |

*Data are presented as the mean ± SD where indicated. Preop ppap indicates preoperative peak pulmonary artery pressure; preop mpap indicates preoperative mean pulmonary artery pressure.

### *Postoperative Management*

In this study, we did not prefer postoperative sedation routinely. We used a direct pulmonary artery catheter in patients whose postrepair mean pulmonary artery pressure was higher than 50% of their mean systemic arterial pressure. We decided to use sedative agents (midazolam, fentanyl, morphine, and pancuronium), sildenafil, and intravenous iloprost according to the postoperative course of pulmonary artery pressure.

### *Pulmonary Hypertensive Crisis*

Pulmonary hypertensive crisis was defined as an acute rise in pulmonary pressure which causes cardiopulmonary compromise as reflected by desaturation and hypotension.

### *Statistical Analysis*

Data were analyzed with the Statistical Package for Social Sciences version 16.0 (SPSS, Chicago, IL, USA). All data were expressed as mean ± standard deviations. The Kolmogorov Smirnov test was used to assess the normal distribution of variables. Pearson and Spearman tests were used for correlation analysis. T tests and Mann Whitney U tests were used in the comparison of groups. Linear regression analysis with the enter method was performed for comparison of statistically significant factors. A $P$ value of .05 was considered statistically significant.

## RESULTS

A total of 201 patients were enrolled in this study. 133 (66.1%) patients were male and 68 (33.9%) patients were female. Mean age was 18.28 ± 16.84 (min: 1; max: 72) months and mean weight was 8.51 ± 4.08 (min: 3.4; max:

Table 2. Multivariate Logistic Regression Analysis of Parameters Which Were Significantly Correlated with Peak and Mean Pulmonary Artery Pressure

| Parameter | Linear Regression Analysis for PPAP OR (95% CI) | P | Linear Regression Analysis for MPAP OR (95% CI) | P |
|---|---|---|---|---|
| RDW | -0.47 (-1.649-0.786) | .485 | -0.088 (-1.474-0.296) | .190 |
| NLR | 0.232 (5.774-20.139) | <.001 | 0.280 (6.229-16.659) | <.001 |
| CRP | 0.265 (12.382-36.490) | .004 | 0.242 (7.525-27.207) | .001 |
| Age | 0.435 (0.429-0.489) | <.001 | 0.413 (0.292-0.555) | <.001 |

RDW indicates red blood cell distribution width; NLR, neutrophil to lymphocyte ratio; CRP, C-reactive protein; PPAP, peak pulmonary artery pressure; MPAP, mean pulmonary artery pressure.

22) kilograms. Mean systolic pulmonary artery pressure was 71.72 ± 23.40 (min: 34; max: 125) mmHg and patients' mean pulmonary artery pressure was 47.64 ± 17.10 (min: 25; max: 89.7) mmHg. Patients' preoperative characteristics are summarized in Table 1.

Mean neutrophil to lymphocyte ratio was 0.82 ± 0.43 (min: 0.19; max: 2.26), mean RDW was 16.49 ± 2.56 and mean CRP value was 0.23 ± 0.23 (min: 0.03; max: 0.5).

Patient age, neutrophil to lymphocyte ratio, red blood cell distribution width, and CRP were found to be significantly correlated with both preoperative peak and mean pulmonary artery pressures. These data were used for linear logistic regression analysis. Patient age, NLR, and CRP were found to be independently correlated with peak pulmonary pressure ($P < .001$, $P < .001$ and $P = .004$) and mean pulmonary artery pressure ($P < .001$, $P < .001$ and $P = .001$). Results of linear logistic regression analysis are summarized in Table 2.

Patients' postoperative follow-up data were also analyzed. Mean extubation time was 26.91 ± 40.35 (min: 3; max: 313) hours, while mean intensive care unit stay was 42.97 ± 89.31 (min: 24; max: 648) hours. Inflammation markers were not found to be significantly correlated with either intubation time or intensive care unit stay. Only preoperative mean pulmonary artery pressure was found to be significantly correlated with intubation time ($P < .001$). Mortality occurred in six patients: three related to sepsis, two related to low cardiac output, and one related to pulmonary artery hypertensive crisis and sudden arrest. Pulmonary hypertensive crisis occurred in 18 patients. NLR and preoperative mean pulmonary artery pressure were found to be significantly different in this subgroup ($P = .03$, $P = .047$). Iloprost treatment was administered in 57 patients and patients' age, weight, preoperative systolic PAP, mean PAP and postoperative systolic PAP, NLR and CRP were found to be significantly different.

## DISCUSSION

In the present study, we investigated the correlation between inflammation markers and congenital heart disease associated pulmonary hypertension. We also analyzed the relationship between postoperative outcomes and preoperative demographics, hematologic parameters, and pulmonary artery pressures. Our results suggest that pulmonary hypertension is significantly correlated with hematologic inflammation markers such as neutrophil to lymphocyte ratio and RDW.

Congenital heart diseases may cause increased pulmonary blood flow with left to right shunt. On the other hand, some diseases affecting the left heart such as congenital mitral stenosis and anomalous pulmonary venous connection with obstruction can result in postcapillary pulmonary hypertension. In both conditions, pulmonary over-circulation and/or increased pressure in the pulmonary vasculature cause abnormal shear stress, circumferential wall stretch, and endothelial dysfunction [D'Alto 2012].

Schermuly et al showed that inflammation might play a major role in the progression of pulmonary hypertension [Schermuly 2011]. Recent studies have shown that complete blood count test parameters may reflect inflammation. In this regard, neutrophil to lymphocyte ratio has been widely studied in various diseases, in particular cardiovascular processes [Hartaigh 2012; Sawant 2014]. Recently, Yıldız et al reported that neutrophil to lymphocyte ratio was significantly increased in adult patients with PAH compared to healthy subjects [Yıldız 2013]. Consistently, we also found a significant correlation between neutrophil to lymphocyte ratio and pulmonary artery pressure. As activated neutrophils have a crucial role in a majority of inflammatory processes, local pulmonary vascular inflammation may affect neutrophils and also platelets. Yıldız et al found a correlation between the presence of pulmonary hypertension and NLR, but we analyzed the relationship between degree of pulmonary hypertension and NLR and found a positive correlation, suggesting that inflammation increases proportionally with severity of pulmonary hypertension. To the best of our knowledge, the present study is the first one to investigate neutrophil to lymphocyte ratio and severity of PAH in the pediatric population. NLR is nonspecific and could not be used as a diagnostic test, but finding the correlation between NLR and severity of disease may be helpful in patients' follow-up and risk prediction.

Endothelial dysfunction and inflammation may result in platelet activation and thrombosis. Additionally, systemic inflammation in PAH may precipitate platelet activation. Mean platelet volume is a simple and inexpensive method of assessing platelet activation [Bath 1996]. In comparison to smaller platelets, larger ones have more granules and higher thromboxane A2 levels, which aggregate more rapidly with collagen and express more glycoprotein Ib and IIb/IIIa. Previously, Varol et al and Can et al also reported a positive correlation between MPV and PAH in adult patients [Varol 2011; Can 2010].

Red blood cell distribution width is another notable parameter that may be associated with inflammation,

dysfunctional erythropoiesis, iron deficiency, and oxidative stress [Rhodes 2011; Ozsu 2014]. In our study, RDW was found to be significantly correlated with peak pulmonary pressure and mean pulmonary pressure, and similarly with NLR, which may support the relationship of inflammation and pulmonary hypertension.

In our study, patients with CRP levels higher than 0.50 mg/dL were excluded, but CRP variations in normal ranges were found to be significantly correlated with pulmonary artery pressure.

Postoperative outcomes were analyzed retrospectively. Preoperative hematologic indices were not significantly correlated with intubation time and intensive care unit stay. Only preoperative mean pulmonary artery pressure was found to be correlated with intensive care unit stay. In our patient population, mortality occurred in six patients, so we could not perform a correlation analysis due to our inadequate sample size.

Pulmonary artery hypertensive crisis is one of the most dangerous postoperative conditions in congenital cardiac surgery procedures. The most likely causative mechanism is abrupt pulmonary vasoconstriction, causing right heart failure and systemic hypotension, which can result in death from severe tissue hypoxia [Brunner 2014]. In this study, 18 patients had experienced pulmonary hypertensive crisis, and NLR together with mean pulmonary artery pressure were found to be significantly higher in this group. Our sample size is limited to show the role of NLR in the prediction of patients' tendency to pulmonary hypertensive crisis. Similarly, NLR and CRP were found to be significantly higher in patients who required iloprost treatment.

In conclusion, preoperative inflammation markers may help to identify the severity of pulmonary hypertensive disease, but further studies with a larger sample size are needed to determine the predictive role of these markers for postoperative outcomes.

### *Study Limitations*

Small sample size and limited correlational analysis between postoperative outcomes and preoperative hematologic predictors are our limitations. Our sample size also limited us in classifying the patients according to the severity of their pulmonary vascular disease. Late follow-up data to analyze the long-term course of the inflammatory process and its relationship with pulmonary artery pressure would also be of great value.

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