

## **Elucidating the Association Between Pulmonary Vein Stenosis and Gastrointestinal Pathology in Premature Infants**

### **A. Study Purpose and Rationale**

Pulmonary vein stenosis (PVS) is a rare cardiac lesion. The diagnosis of PVS is primarily via echocardiogram—turbulent flow on doppler or via cardiac catheterization. There are two types of PVS: primary and secondary. Primary PVS is only seen in structurally normal heart i.e. it's the only lesion found in the heart. Secondary PVS occurs in structurally abnormal hearts—those with congenital malformations such as total anomalous pulmonary venous return or hypoplastic left heart syndrome (Reidlinger et. al., 2006). Secondary PVS is most frequently seen after surgical intervention (Song et. al., 2013). For the purposes of this study we will focus on primary PVS.

Primary PVS is rarer than secondary PVS. The estimated annual incidence is approximately 1.7 per 100,000 children under the age of two years in one study (Drossner et. al., 2008). This approximate annual incidence is probably an underestimate as many of the published studies demonstrate findings of primary PVS during surgery or autopsy (Bini et., al. 1984). Per Song and colleagues, the initial clinical presentation may be failure to thrive, dyspnea, and subcostal retractions. The course rapidly progresses and is characterized by “recurrent episodes of pulmonary edema, signs of severe right ventricular hypertrophy, and eventually pulmonary hypertension” (Song et. al., 2013). This anomaly is often lethal, and despite advances in medical and surgical treatment of these patients, long-term prognosis remains poor. In fact per Song and colleagues, they determined the median survival was three months between diagnosis and death (Song et. al., 2013).

Due to this condition's rare nature, there is limited published data about the etiology and risk factors. Primary PVS is thought to result from abnormal incorporation of the common pulmonary vein into the left atrium at later stages of cardiac development (Latson and Prieto, 2007). Per Reidlinger and colleagues, the mechanism of PVS described above may explain the “pathophysiology of infancy” but their study included patients diagnosed with primary PVS in childhood and adolescence. They found that primary PVS may be due to the “expansion of the pulmonary venous intima with progressive occlusion of the vessel lumen.” These intimal lesional cells are myofibroblasts like and express various receptor tyrosine kinases (Reidlinger et. al., 2006). However, both Latson and Prieto as well as Reidlinger and colleagues theories of primary PVS pathophysiology could account for its occurrence in infancy, childhood, and adolescent. Prematurity is thought to possibly be a risk factor for the development of PVS (Drossner et.al, 2008). There are many diseases of prematurity including retinopathy and bronchopulmonary dysplasia which are

characterized as an inflammatory response mediated by VEGF. Therefore, it is thought that VEGF may be partly responsible for PVS as well (Drossner et . al., 2008).

A recent retrospective chart review of cases of premature infants with a newly diagnosed PVS was conducted at New York Presbyterian Children's Hospital. Demographic information, prior medical history, presenting signs and symptoms, methods of diagnosis, hospital course, echocardiographic data, hemodynamic and angiographic data from cardiac catheterization, intervention and mortality were reviewed in patient records. 20 premature infants from 2006 to 2012 were included in the study. Of these 20 premature infants, 45% of these patients with acquired PVS previously had necrotizing enterocolitis.

However, there is lack of data with regard to the relationship between PVS and gastrointestinal pathology in preterm infants, but we have observed that many infants with PVS have associated gastrointestinal pathology such as omphalocele and necrotizing enterocolitis (the mechanism of this relationship remains to be determined). Interestingly the association between PVS and gastrointestinal pathology may lie in the embryonic origins of the pulmonary veins as the primordial venous system is part of the splanchnic plexis, which initially connects to the cardinal and umbilical veins (Latson and Prieto; 2007, Sadler, 2000).

The goal of this research endeavor is to further investigate the relationship between PVS and gastrointestinal pathology based on the prior case report series completed at New York Presbyterian Hospital. Based on the case report series there appears to be a significant relationship between PVS and gastrointestinal pathology. If there is indeed a statistically significant association we hope to better understand risk factors and propose a screening protocol to better elucidate the timing and progression of these conditions and afford the opportunity for early diagnosis and therapy in patients with PVS who develop gastrointestinal pathology such as omphalocele and necrotizing enterocolitis.

## **B. Study Design and Statistical Analysis**

This research endeavor is designed as a non-randomized retrospective case-control series investigating the relationship between PVS and gastrointestinal pathology. In this study we will include premature infants (less than 37 weeks gestational age) with a new diagnosis of PVS based on echocardiographic data as well as hemodynamic and angiographic data from cardiac catheterization (if applicable). Of these patients with PVS we will investigate if the patients develop any gastrointestinal pathology based on presenting signs and symptoms and radiographic data during the hospital course.

We plan to review and report on the existing data available for this series of patients from their medical records. The data collected will include: demographic information, prior

medical history, presenting signs/symptoms, method of diagnosis, hospital course, echocardiographic data, hemodynamic and angiographic data from cardiac catheterization if applicable, intervention (if any was performed), and mortality.

Necrotizing Enterocolitis (NEC) was defined according to modified Bell's staging Criteria II or III (Gordon et.al. 2007). Primary PVS was diagnosed by an abnormal flow pattern that was turbulent and continuous, as opposed to normal flow pattern with well-defined systolic and diastolic peaks on mean pulse wave doppler gradient  $>3\text{mmHg}$ . In isolated cases, diagnosis was made either by MRI or cardiac catheterization.

We plan to match three control patients (60 premature infants without PVS) from the NICU census log based on a time period similar to the patient's birth and gestational age with patients with PVS as a comparison to determine if there is an association of PVS with gastrointestinal pathology. Using a chi-squared test with a power of 0.8 and alpha of 0.05, the prevalence of gut pathology in patients without PVS needs to be less than 6.9% to demonstrate significance between PVS and gut pathology in premature infants.

### **C. Study Procedures**

A retrospective chart review will be performed for the identified cases of infants who presented with a new diagnosis of pulmonary vein stenosis. The data described above will be collected from the existing medical records. The patients' identifying information will be removed from the data, and a unique study ID number will be assigned to each patient; a separate password-protected file will correlate the patient identifiers to the study ID numbers and will be accessible only to the study personnel.

D. **Study Drugs:** Not applicable.

E. **Medical Devices:** Not applicable.

F. **Study Questionnaires:** Not applicable.

### **G. Study Subjects:**

The study subjects will be premature infants (gestational age  $<37$  weeks) who presented to New York-Presbyterian Hospital with a new diagnosis of pulmonary vein stenosis and gastrointestinal pathology. The controls will be premature infants without PVS matched for gestational who were admitted to the NICU during the same time period (within two to four weeks).

Inclusion criteria include neonates with gestational age <37 weeks in the NICU between 2006-2012. Exclusion criteria neonates diagnosed with congenital heart defects such as total anomalous pulmonary venous return or hypoplastic left heart syndrome, gestational age >37 weeks, control patients without an echocardiogram, and neonates with prior cardio-thoracic surgery involving the region of the pulmonary veins.

- H. **Recruitment of Subjects:** Not applicable.
- I. **Confidentiality of Study Data:** Patient confidentiality will be maintained, as all data will be de-identified and given a unique study ID number. There will be a separate password-protected file linking the patient identifiers to the study ID numbers, which will be stored on a computer in a secure location. All study materials will also be kept in a secure location, accessible only to the study investigators.
- J. **Potential Conflicts of Interest:** None
- K. **Location of the Study:** The Neonatal Intensive Care Unit of New York-Presbyterian Hospital.
- L. **Potential Risks:** As this is a retrospective review of medical records only, there are no potential risks to study subjects (other than risk to patient confidentiality, which will be minimized as above).
- M. **Potential Benefits:** There are no potential benefits to study subjects, as this is a retrospective chart review only. The information gained, however, could potentially impact the future care of other infants who are born prematurely and/or have pulmonary vein stenosis.
- N. **Alternatives Therapies:** Not applicable.
- O. **Compensation to Subjects:** None.
- P. **Costs to Subjects:** None.
- Q. **Minors as Research Subjects:** The study involves premature infants in the Neonatology Intensive Care Unit at New York Presbyterian Hospital. However, due to the retrospective chart review protocol, their direct participation is not required.

**R. Radiation or Radioactive Substances:** Not applicable.

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