Association between pulmonary vein stenosis and necrotizing enterocolitis or gastrointestinal pathology: A case–control study

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ABSTRACT

Objective	:	Pulmonary vein stenosis (PVS) is an emerging cause of pulmonary hypertension in preterm infants. It is an often lethal condition with poor long-term prognosis and high mortality. Previous work suggests an association between necrotizing enterocolitis (NEC) and PVS, supporting a possible role for inflammatory processes due to gastrointestinal (GI) pathology as an associated risk factor for PVS.
Study Description	:	We performed a matched case–control study where infants with PVS were matched for gestational age with infants without PVS. Hospital records were reviewed for prior history of NEC or other gut pathology.
Results	:	Twenty-four PVS patients were matched with 68 controls; 63% of patients (15/24) had prior GI pathology as opposed to 19% (13/68) of controls. The GI pathology group had a significantly higher growth restriction and C-reactive protein. The mean gradient across the pulmonary veins was higher in the gut pathology group versus controls, as was mortality (29% vs. 9%).
Conclusions	:	The previously described association between PVS and intestinal pathology was further strengthened by this study. The presence of GI pathology should lead to early surveillance and intervention for PVS.
Keywords	:	Gut pathology, necrotizing enterocolitis, pulmonary vein stenosis

INTRODUCTION

Pulmonary vein stenosis (PVS) has emerged as a cause of pulmonary hypertension (PH) in preterm infants and has been described in association with bronchopulmonary dysplasia (BPD).[1-5] Recent reports have suggested an association between necrotizing enterocolitis (NEC) and PVS, but this association has not been further explored thus far.[5-7] The narrowing of one or more pulmonary veins occurs either at its entry into the left atrium or further into the lungs and is caused by fibromuscular proliferation in the intima and media of the veins. Physiologically, this obstruction to pulmonary venous return leads to increase in back pressure to the pulmonary capillaries and pulmonary

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arterioles, resulting in PH. It can present in association with congenital heart lesions such as total anomalous pulmonary venous return or hypoplastic left heart syndrome or occur in preterm infants with BPD. In preterm infants, PVS is often progressive, involving multiple veins, and has been associated with poor long-term prognosis and high mortality. Risk factors have not been clearly defined for this lesion; however, studies suggest that an inflammatory process may cause intimal proliferation leading to stenosis of the pulmonary veins.[1,8]

In premature infants, NEC is an important cause of morbidity and mortality, with an estimated incidence of 2%–10% in very low birth weight infants.[9-11] The mortality associated with NEC ranges between 20% and 50%, with the highest mortality seen in those infants who required surgical intervention for their NEC. The etiology of NEC is usually multifactorial, with the interaction of several components such as intestinal dysbiosis, ischemic events, and an exaggerated inflammatory response mounted by intestinal epithelial cells leading to the clinical disease that is NEC. A similar inflammatory state is noted in PVS and may be mediated by vascular endothelial growth factor (VEGF), which has also been suggested as an associated factor retinopathy of prematurity (ROP).[11,12]

We previously reported a case series of 21 premature patients with acquired PVS, ten of whom were noted to have NEC during their neonatal intensive care unit (NICU) course.[6] We speculated that there may be an association between the development of PVS and NEC or gastrointestinal (GI) pathology or inflammation in preterm infants. To explore this association, we performed a case–control study expanding on our previous data and adding matched control patients from the same era.

MATERIALS AND METHODS

A nested, matched case–control study was performed using preterm infants diagnosed with PVS from echocardiogram at our institution from January 2006 to July 2013. Hospital records of these subjects were reviewed for gestational age, birth weight, age at diagnosis of PVS, history of NEC or gut involvement, and the time of diagnosis. Serial echocardiograms were reviewed for progression of PVS and PH [Figure 1]. Neonates diagnosed with total anomalous pulmonary venous return or hypoplastic left heart syndrome were excluded, as these conditions are known to have a significant association with congenital PVS. Infants ≥37 weeks' gestation were also excluded.

Control infants were selected from a cohort at our institution participating in a multicenter study, the
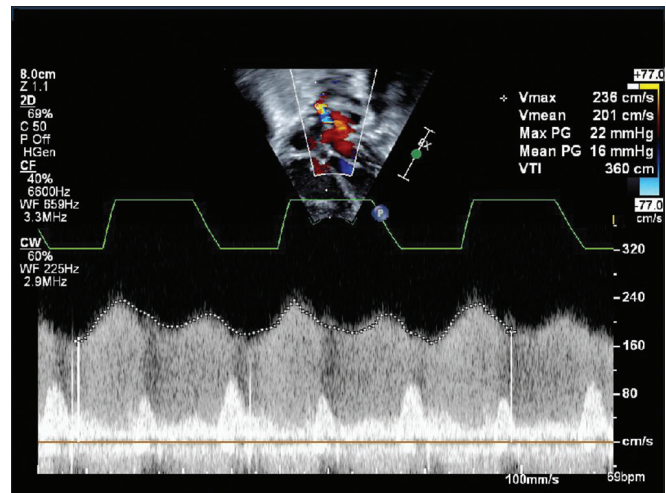

Figure 1: Echocardiogram with color Doppler demonstrating flow acceleration in the upper pulmonary vein. Continuous-wave Doppler demonstrating the peak and mean gradients across the pulmonary vein

Interdisciplinary NICU Antimicrobial Prescribing (iNAP). The iNAP cohort was enrolled between May 2009 and April 2012. Eligible infants were any infants admitted to our NICU at <7 days of age on admission who were hospitalized for >4 days. Demographics, diagnoses, selected laboratory, and radiologic data and detailed antibiotic use data were collected. Infants enrolled in the iNAP study who served as control subjects did not carry a diagnosis of PVS during their NICU hospitalization. This was a blinded sample of existing data; only parameters that were collected at the time of the original iNAP study could be utilized to compare with the PVS cohort. This substudy utilized this existing cohort, examined treatment and outcomes of NEC, and was approved by the Institutional Review Board with a waiver of informed consent.

Study definitions

The primary exposure variable was GI pathology. GI pathology was defined as conditions such as medical and or surgical NEC, omphalocele, intestinal atresias, or congenital diaphragmatic hernia. NEC was defined using the Center for Disease Control and Preventions' National Healthcare Safety Network criteria.[13] GI pathology, if present, always preceded the diagnosis of PVS. PVS was diagnosed by echocardiogram done either for clinical suspicion for worsening PH or for evaluation for cardiac shunts. PVS was defined as an abnormal Doppler flow pattern that was turbulent and continuous, as opposed to the normal flow pattern with well-defined systolic and diastolic peaks, and a mean pulse wave Doppler gradient >3 mmHg (the measurement was confirmed by continuous-wave (CW) Doppler). Pulse wave Doppler was used to determine the location of the measured velocities allowing for determination of the location, and CW Doppler measurement was used

to estimate the gradient. All four pulmonary veins were visualized as possible, and the location of stenosis and gradients were charted. Presence of absence of a patent ductus arteriosus (PDA) and other shunts, their direction, and gradients was also noted. Available infant data were reviewed for demographic variables and patient characteristics as well as for documentation of additional inflammatory disease states including ROP, as defined by ROP Stage 2 or greater or any ROP-requiring intervention. BPD was defined as a requirement for respiratory support or oxygen support beyond 36 weeks postmenstrual age.[14]

For the majority of subjects, PH was determined based on echocardiogram findings of TR gradient (when available), flattening of the interventricular septum, and bidirectional or right to left shunting at the PDA. In our institution, when the diagnosis of PH is made or suspected, echocardiographic evaluation by protocol includes assessment of PVS in all four veins and follow-up echocardiograms continue to evaluate the pulmonary veins, particularly in cases where PH is resistant or fails to improve with standard PH therapy. Other causes of worsening PH including lung parenchymal issues, gastroesophageal reflux, micro-aspiration, and infections are also assessed and treated as appropriate in each patient.

Study design

The 1:3 case to control matching was performed by gestational age (within 2 weeks) as well as time of admission in order to match treatment protocols in existence. When there were more than three eligible control subjects for a case subject, those with an admission date closest to the admission date of the respective case were selected. Infants with congenital heart disease with a known association with PVS were excluded. Control infants did not carry a diagnosis of PVS and/or had no evidence of PVS on echocardiogram. Decisions to repeat echocardiograms were based on the treating medical team caring for the infant.

Statistical analysis

Descriptive statistics were performed to explore the distribution of variables of interest, including demographic characteristics, prior inflammatory states, and evidence of infection and/or inflammation. Bivariate analyses were performed using Student's *t*-test or Wilcoxon rank-sum for continuous variables and Chi-squared or Fisher's exact tests for categorical variables as appropriate. Exposure variables with $P < 0.05$ or felt to be a variable of strong biologic plausibility were entered into a multivariable conditional logistic regression model. Collinearity was evaluated by examining the variance inflation factors of variables of concern. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for analysis.

RESULTS

Twenty-four infants with PVS were matched with 68 controls (for a 1:3 case–control study). For four infants, only two matched controls could be found. Of these four infants, three had a gestational age of <27 weeks and a birth weight of <750 g. Table 1 shows the unadjusted comparison of demographic variables and clinical variables between cases and controls.

Of the cases, 11 had baseline normal echocardiograms documented prior to the diagnosis of PVS. Ten cases were transferred from other institutions, 5 of which had a prior echo without PVS documented. The majority of both cases and controls with GI pathology had NEC, 11 (46%) from the case group (all prior to diagnosis of PVS) and 11 (16%) from the control group. In unadjusted analysis, persistent PH, BPD, and maximum C-reactive protein (CRP) were significantly different between cases and controls. PDA, ROP, and culture-proven sepsis were not significantly different between the cases and controls [Table 1].

Infants had initially received targeted pulmonary vasodilator therapy including inhaled nitric oxide, sildenafil, or bosentan for their PH. Treatment varied based on the etiology and severity of the PH and the extent of PVS contributing to the PH. If PVS was considered as a significant contributor to the PH, pulmonary vasodilators were weaned off as they could increase pulmonary edema and worsen the clinical status.

Three patients with NEC underwent surgery for NEC and the others were treated medically. Five patients in the entire cohort underwent surgical repair of the

Table 1: Univariate comparison of variables between case and control subjects

Variable	Case (*n*=24)	Control (*n*=68)
Demographic data		
Birth weight (g), median (IQR)	1154 (505-1790)	1329 (745-1780)
Gestational age (weeks), median (IQR)	29 (26-33)	29 (27-33)
Male sex, *n*(%)	7 (29)	35 (52)
Clinical variables		
GI pathology*	16 (67)	13 (19)
NEC	11 (46)	11 (16)
Omphalocoele	1 (4)	1 (1.5)
Other[a]	4 (17)	1 (1.5)
Culture proven sepsis	6 (25)	13 (19)
CRP max* (mg/dl), median (IQR)	94 (14-160)	33 (0.75-33)
ROP	8 (34)	10 (15)
BPD*	15 (63)	21 (31)
PDA[b]	15 (63)	34 (67)
PH[b]*	24 (100%)	11 (22)
Death*	7 (29)	7 (10)

*Significant *P*<0.05, [a]Surgery for CDH, intestinal atresia, [b]Of infants who had echocardiograms. IQR: Interquartile range, GI: Gastrointestinal, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia, PH: Pulmonary hypertension, CRP: C-reactive protein, PDA: Patent ductus arteriosus, CDH: Congenital Diaphragmatic Hernia

PVS. Two were in the NEC group, one of whom showed improvement and one who died from progression of the disease. Three were in the non-NEC group, with two showing improvement and one was lost to follow-up. In the NEC group as a whole, one patient showed improvement in their PVS after surgical repair, four had improvement in gradient or were unchanged over a mean follow-up of 6.5 months, three died from progression of the PVS with uncontrolled PH, and one infant died from septic shock. In the non-NEC Group, two patients improved after surgical repair, two patients improved spontaneously with a mean follow-up of 26 months, two were unchanged over a mean period of 32 months, two died from progression of their PVS and refractory PH, and two patients died from septic shock. Improvement was determined by follow-up echocardiograms that showed decreasing gradients across the pulmonary veins. Since medical treatment modalities were not available at the time the data were collected, none of the patients received advanced medical therapies currently available.

Several exploratory multivariable models were tested with the variables available; in all models, prior GI pathology was the only variable that remained significant. PH and PDA, which have a biologically plausible relationship with PVS, displayed co-linearity. In the final model, which comprised the variables of GI pathology and BPD, GI pathology showed a significant association with PVS (odds ratio 10.3, 95% confidence interval 2.9, 36.9).

DISCUSSION

PVS has been increasingly recognized as a complication in preterm infants with BPD and is associated with significant morbidity and mortality. In recent years, aggressive management both by transcatheter intervention, early surgery, and medications to delay or prevent restenosis has shown promise with reduction in mortality.[8,15-18] It is well established that prematurity and BPD are risk factors for the development of acquired PVS.[1,5,9] The association between GI inflammation and PVS was first described in a case series published by our team in 2014 and subsequently also found in other multicenter retrospective case series.[6,7] The current paper establishes that GI pathology is a strong risk factor for the development of PVS in preterm infants with BPD, using the original cohort and using 3:1 controls from the same era. While NEC was the diagnosis of GI inflammation in a majority of infants, other pathologies including omphalocele, gut surgery with associated inflammation, were seen in a minority. This varied GI pathology suggests that it is not only NEC but also inflammation or surgical instrumentation in any form could be an impetus in development of pulmonary vein pathology.

Prematurity is also known to be the most common risk factor for NEC, with the risk being inversely related to birth weight and gestational age. While the exact pathophysiology of NEC is not well known, it is hypothesized that due to intestinal tract immaturity, bacterial dysbiosis, and a disrupted immune response, there is an inappropriate response to any intestinal injury.[19] This results in an exaggerated inflammatory response mounted by immature intestinal epithelial cells. Banyasz *et al.* found that a carrier state for a mutant allele of VEGF, an important protein involved in angiogenesis, is an independent risk factor for NEC.[11,12,20,21] A study published by Riedlinger *et al.* focused on the histology of acquired PVS.[12] Their findings suggested that intimal lesions are the result of a myofibroblast-like proliferation, with this process being mediated in part by expression of receptor tyrosine kinases, such as VEGF. This might suggest a common inflammatory origin to both NEC and acquired PVS and would be a basis for future testing and management options. We noted a trend toward a more elevated CRP in those infants who developed PVS, once again suggesting that active inflammation plays a role. VEGF is also hypothesized to mediate the pathologic vessel growth seen in two additional diseases of the premature infant, ROP and BPD.[22] In BPD, VEGF has been implicated in abnormal development and remodeling of the pulmonary arterial and venous beds. This same process may, in fact, be present in the development of PVS in premature infants. Indeed, these associations have led to studying the use of VEGF inhibitors and biologic agents to treat progressive PVS in the hope of halting progression or recurrence after intervention.[9,23] Callahan *et al.* describe the use of a combination of imatinib mesylate with or without bevacizumab for the treatment of multivessel intraluminal PVS. Such targeted therapies selectively target those cells responsible for the intimal cellular proliferation associated with progressive PVS.[23] Sirolimus, a mTor inhibitor, is another medication that is currently being evaluated for use in halting the progression of PVS.[24] Very close surveillance, aggressive surgical or transcatheter intervention in combination with medical therapies show promising results that in the future may change the progression/deterioration of PVS.[23,24]

Elegant studies by Hall *et al.* have suggested that the pulmonary veins originate from the splanchnopleural mesoderm with vasculogenesis induced by VEGF.[25] We speculate that since there is a common embryologic origin to splanchnic vasculature and pulmonary veins, VEGF-mediated inflammation in one system might affect cells with similar embryologic origins in the other system. We speculate that the inflammatory process associated with NEC may also contribute to the endothelial proliferation described in PVS. Other studies have also shown that infants have been documented to have had multiple echocardiograms showing unobstructed pulmonary veins before stenosis

becomes manifest, once again suggesting a triggering factor to initiate the intimal proliferation obstructing the veins.[7]

Similar to prior studies, there were a few infants with PVS in the current study, who also had simple cardiac shunts at the atrial or ductal level.[7] It is possible that left to right shunts with excessive pulmonary venous return in the presence of other inflammatory comorbidities in a premature infant predispose the development of PVS from excessive flow and shear stress within the veins, leading to speculation that perhaps early shunt closure in preterm infants might reduce the impetus for PVS.

There are several limitations to this series. This was a retrospective single-institution case–control study, thus the number of subjects was limited. A sample size calculation was not performed; however, a *post hoc* power calculation did reveal that our sample size with even a 1:2 matched control provided ~80% power to detect an increased odds of 4.5 of PVS given the primary exposure. As in many studies with limited sample size, the possibility of a Type II error exists, for example, failing to detect an association between PVS and other biologically plausible exposures such as ROP and sepsis. There are limited data on both NEC and prior echocardiogram in infants who presented as transfers to our institution at an older age. Since data collection for both case and controls were censored by December 2013, we have not explored the longer-term outcomes of these infants, especially in the era of aggressive medical, surgical, and transcatheter intervention. In addition, specific data on the control subjects were limited to that collected as part of the iNAP study and did not include details regarding feeding mode while on antimicrobials. Clinical care and decisions regarding feeding, duration of antibiotics, and other clinical decisions, were made by the treating neonatal team based on the infant's clinical status. Not all infants with GI pathology underwent surgery and the number of infants with omphalocele was small in both the case and the control groups, with only one subject with omphalocele in each group. As a result, it is not possible to generalize these findings to infants with omphalocele. The retrospective format of this study and lack of an echo protocol for aggressive screening of preterm infants with NEC at the time preclude documentation of the exact interval between the triggering event (NEC) and start of PVS. It is well known that in PVS, echocardiogram and Doppler are only screening tools, and gradients obtained on Doppler are not accurate because of the angle of Doppler with respect to the stenosis and tortuosity of the pulmonary veins; hence, further details of gradients were not analysed [Figure 1 demonstrates this]. Echocardiograms were not done on all controls in this study. During the time period of the study, PDA closure was not routinely performed. All preterm infants did not get routine echocardiograms, and at that time, it was not routine to perform echocardiograms on preterm infants with GI pathology. The majority of high-risk deliveries that are admitted to the NICU have had fetal echocardiograms documenting segmental anatomy and ruling out significant congenital heart disease, further limiting the number of routine echocardiograms that are done. From chart review, none of the control infants had any suspicion of PVS mentioned. However, 12/13 control infants with GI pathology did have echocardiograms performed for various reasons, none of which revealed PVS. Since most infants in this study did not undergo cardiac catheterization or advanced cross-sectional imaging, the relationship between NEC and gradients and the length or degree of stenosis could not be conclusively obtained. In the current era of more extensive imaging and early intervention, this association should be further explored.

CONCLUSIONS

Acquired PVS is an often-lethal anomaly with a poor long-term prognosis. Prematurity is a known risk factor for its development. In this case–control study, we have established the association between NEC and GI pathology and the development of acquired PVS. We suggest that in preterm babies who develop clinical or echocardiographic evidence of PH, especially those with NEC or GI inflammatory pathology, there should be a high index of suspicion for development of PVS. A protocol should be developed to obtain detailed echocardiographic screening studies at frequent intervals in high-risk infants followed by advanced cross-sectional imaging including computed tomography angiograms or magnetic resonance angiograms if PVS is noted on screening echocardiogram to characterize the degree and the anatomy of PVS.[26] This should provide enough information for decision making and referral for either interventional catheterization or surgical repair, in a timely manner. Medical specialists caring for infants/children with PH should have a high index of suspicion for PVS and consider obtaining subsequent diagnostic studies, as in some cases, earlier treatment and/or treatment with biological agents holds promise and may improve survival outcomes. This will also allow for more detailed investigation into the role of medical therapy to prevent progression or recurrence of PVS in these infants after the initial intervention.

What is already known on this topic

PVS is associated with prematurity and BPD. Association between PVS and intestinal pathology including NEC has been suggested but has not been studied in depth thus far.

What this study adds

This 1:3 case–control study establishes the association between PVS and NEC or intra-abdominal inflammatory pathology.

Institutional Review Board approval

- Columbia University IRB approval number-AAAC-6366 (iNAP study for controls); AAAI1839 (PVS in preterm infants)
- The study was performed in accordance with the Declaration of Helsinki.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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