Are We Really Getting Any Better, and If Not, How Might We Do it?

Extremely Rare and Highly Variable: Pulmonary Vein Disease

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Disclosures

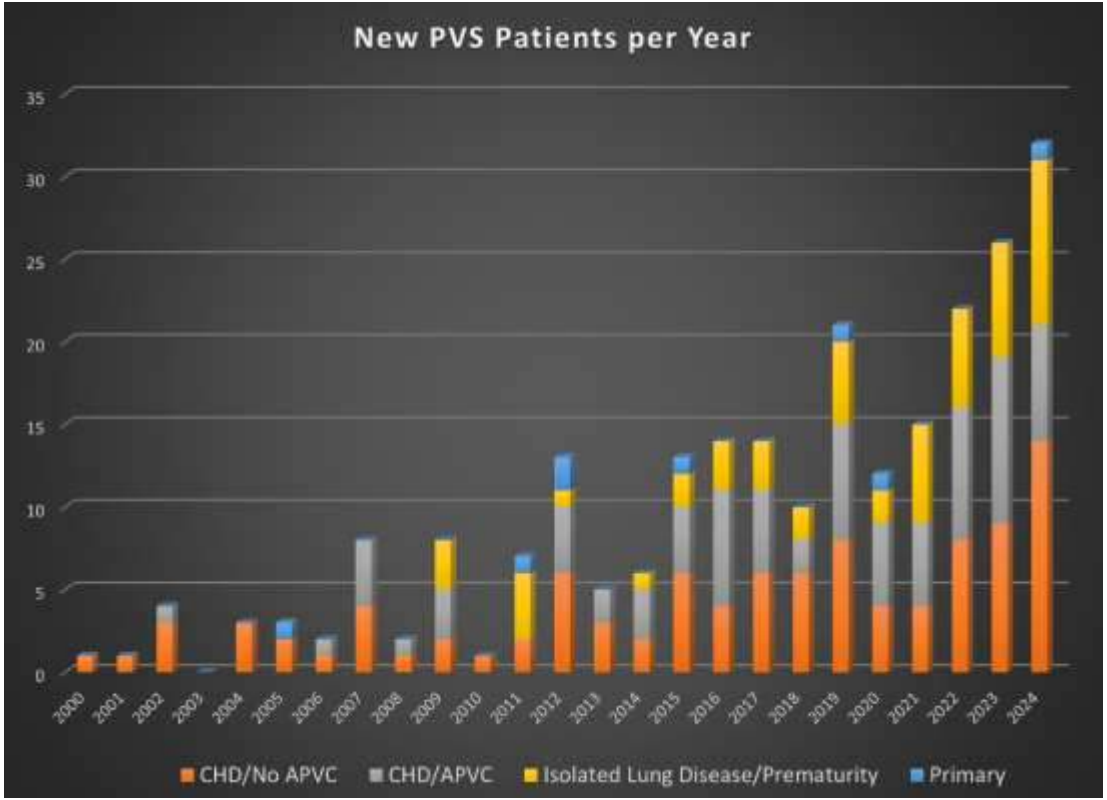
- None

- Are we really getting any better?
  - **YES**
  - (How = Objective #1)
- Can we do better?
  - **ABSOLUTELY**
  - (How = Objective #2)

How are we getting better?

1. Diagnosis
2. Management

New PVS Patients per Year (CHOP)



Age at PVS dx

- 2024: med 9 mo [3,81]
- 2025: med 5 mo [3,14.5]
  - 41% (13/32) single vessel at diagnosis

Screening High Risk Patients

PVS associated with Prematurity

- 5% of severe BPD patients
- Associated with earlier gestation, IUGR, prolonged mech ventilation, NEC

Heching HJ et al. Arch Dis Child Fetal Neonatal Ed 2014.
Swier NL et al. Am J Perinatol 2016.
Drossner DM et al. Pediatrics 2008.
Zettler E et al. *J Perinatol* 2020.

Screening

-Monthly echo for mod/severe BPD*

-Echo for worsening (or failure to progress) resp status of unclear etiology

*Jensen EA et al. Am J Respir Crit Care Med 2019.

Table II. Multivariable model of clinical variables associated with PVS in infants with sBPD

Clinical variables	Odds ratios (95% CI)	*P*-value
Gestational age (wks)		
22-≤24	0.7 (0.3, 1.3)	.19
25-≤27	0.5 (0.2, 0.9)	.01*
≥28	REF	
Small for gestational age (weight <10% at birth)	2.1 (1.3, 3.6)	<.01*
Surgical necrotizing enterocolitis	5.1 (2.4, 10.6)	<.01*
Atrial septal defects	2.1 (1.2, 3.9)	<.01*
Pulmonary hypertension	6.2 (3.7, 10.5)	<.01*

Table IV. Multivariable model of infants on mechanical ventilation at 36 weeks' PMA (n = 102)

Clinical variables	Odds ratios (95% CI)	*P*-value
Gestational Age (weeks)		
22-≤24	0.8 (0.4, 2.0)	.75
25-≤27	0.7 (0.3, 1.6)	.36
≥28	REF	
Mechanical ventilation at 36 wks PMA	4.3 (1.8, 12.9)	<.01*

McArthur E et al. *The Journal of Pediatrics* 2024.
3:1 case control trial from pool of 10171 patients.
PVS prevalence = 1.1%

Screening High Risk Patients

Repaired TAPVC

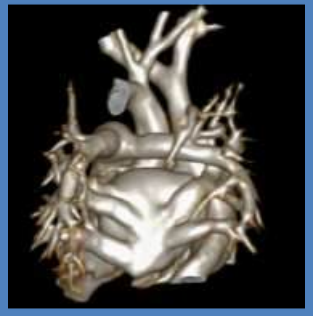
- ~15% develop pulmonary venous obstruction
- Spectrum
  - Silent unilateral atresia
  - FTT, respiratory failure

Seale AN et al. Circulation 2010.

Screening

-Cross-sectional imaging (ideally cMRI) within 3 months of repair

-Identify at risk vessels



Sengupta A et al. Ann Thorac Surg 2022.

TABLE 4 Final Risk Prediction Model for Late Unplanned Transcatheter or Surgical Reintervention

Predictor	SHR (95% CI)	*P* Value
PV residual lesion[a]		
Class 2 (minor)	4.8 (2.8-8.1)	<.001
Class 3 (major)	6.4 (3.5-11.7)	<.001
Age[b]		
Neonate or infant (<1 y)	3.3 (1.3-8.5)	.014
Preoperative obstruction	1.8 (1.1-2.8)	.015

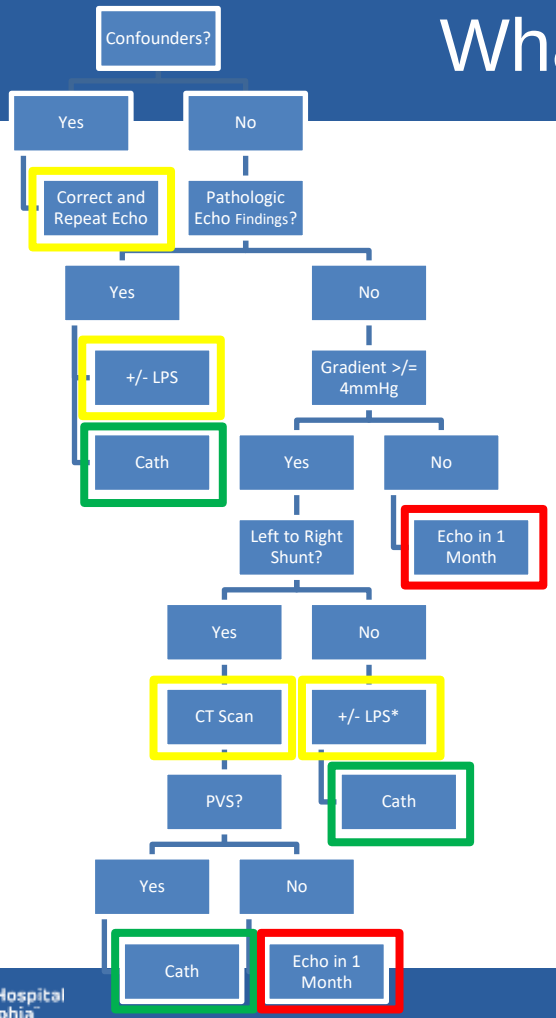
[a]PV residua based on the predischarge echocardiogram, with class 1 (no/trivial residua) as the reference group; [b]1 year of age and older as reference. The final risk prediction model for late reintervention was comprised of clinically relevant variables that were significant at the 0.05 level on previous multivariable analysis. The C-index for this model was 0.764. PV, pulmonary vein; SHR, subdistribution hazard ratio.

SUBCOMPONENT SCORE

Class 2 (Minor Residua)

Mild Obstruction; MG 2-4 mmHg

What do to with new Echo gradients?



Confounders

- Tachycardia, anemia, high output state, fetal transitioning

Pathologic Echo Findings

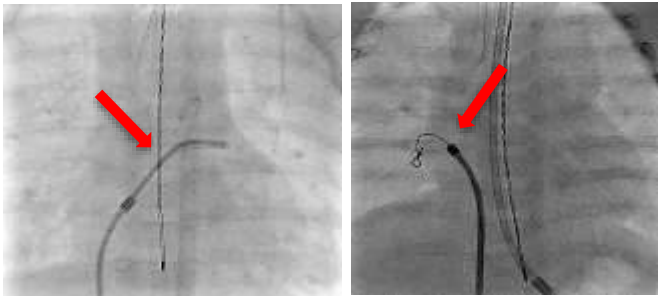
- Doppler with loss of phasic variability
- New or worsening RV HTN or RV dysfunction w/o secondary cause (infection, acidosis, etc.)

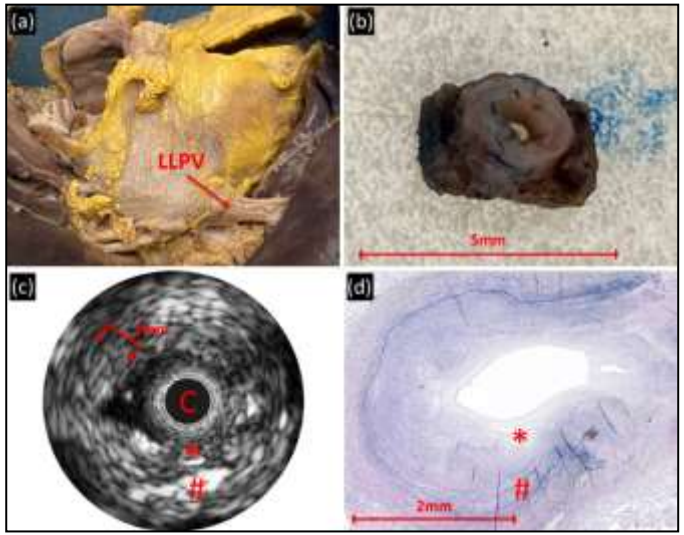
*Reasonable to observe only if single vein gradient and preserved LPS flow

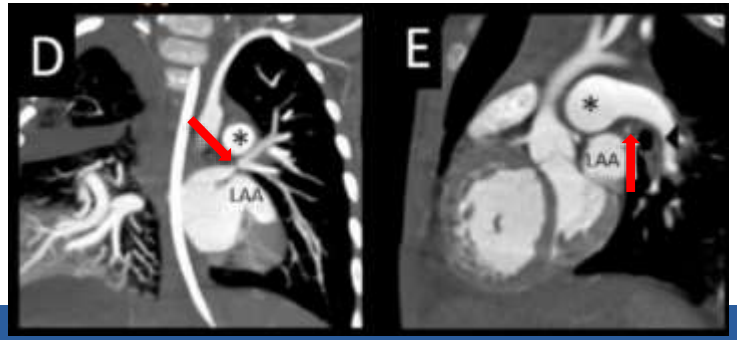
- repeat echo/LPS in 1-month if risk factors for progression (h/o SGA, PH, NEC, aspiration, mech vent at 36 weeks PMA)

Confirming PVS

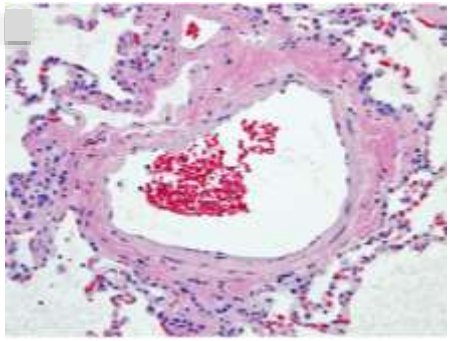
Pediatric intraluminal pulmonary vein stenosis (**PVS**) is a disease of wall thickening (neo-intimal proliferation) leading to luminal narrowing -> pulm edema -> PH -> RH failure

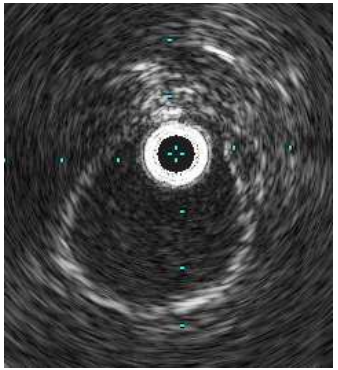






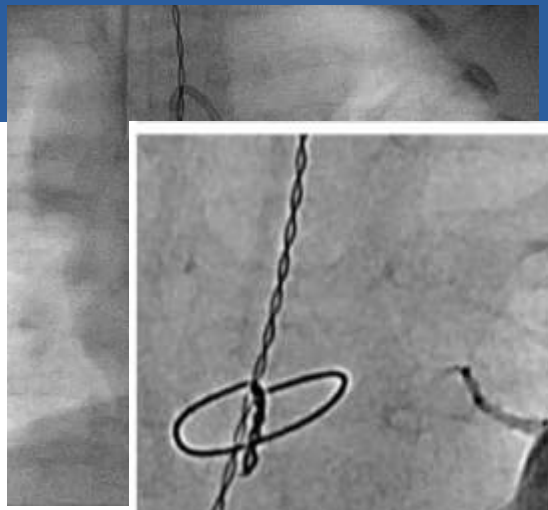
Normal Vein

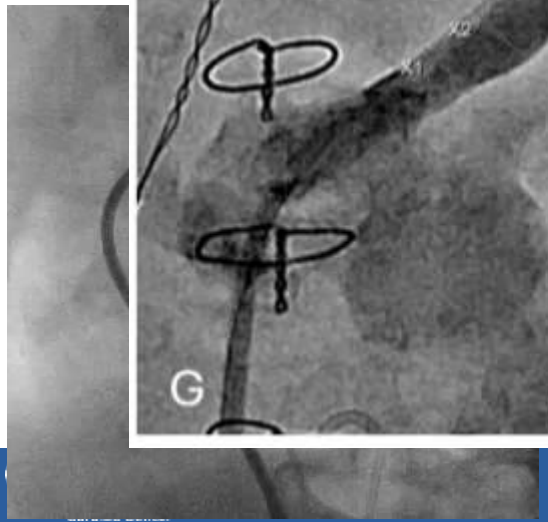




Callahan R, et al Children 2021.
Sena L, et al Children 2021.

Confirming PVS

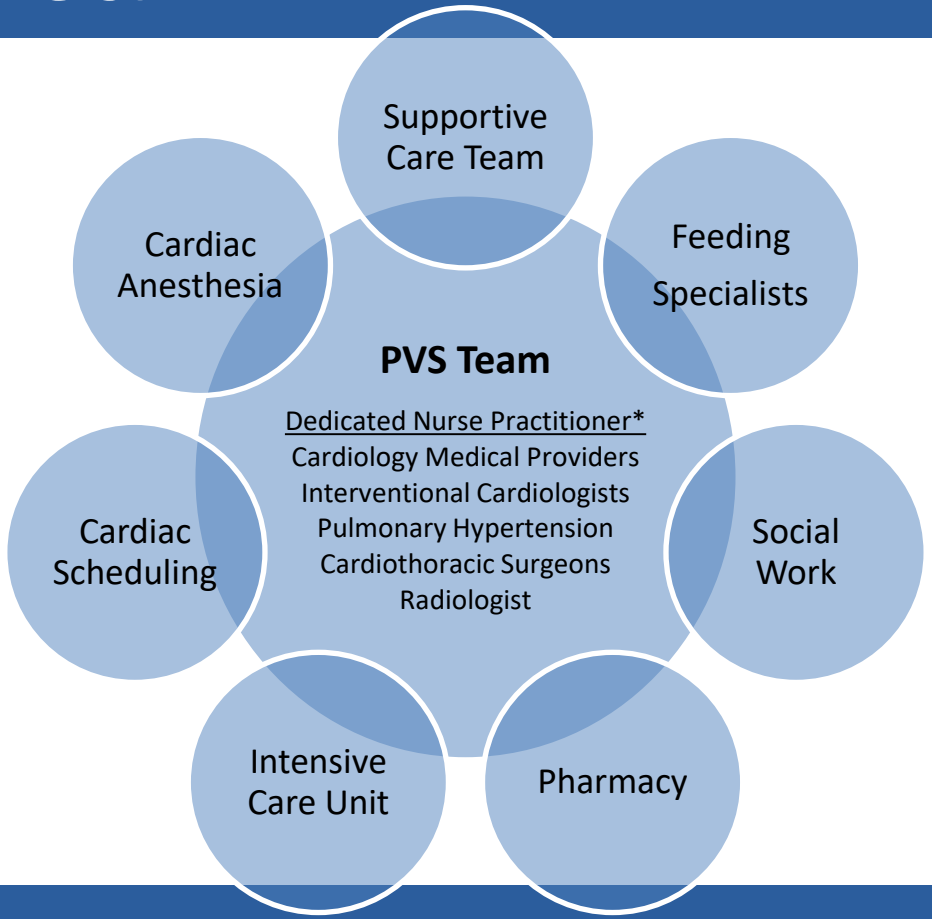




How are we getting better?

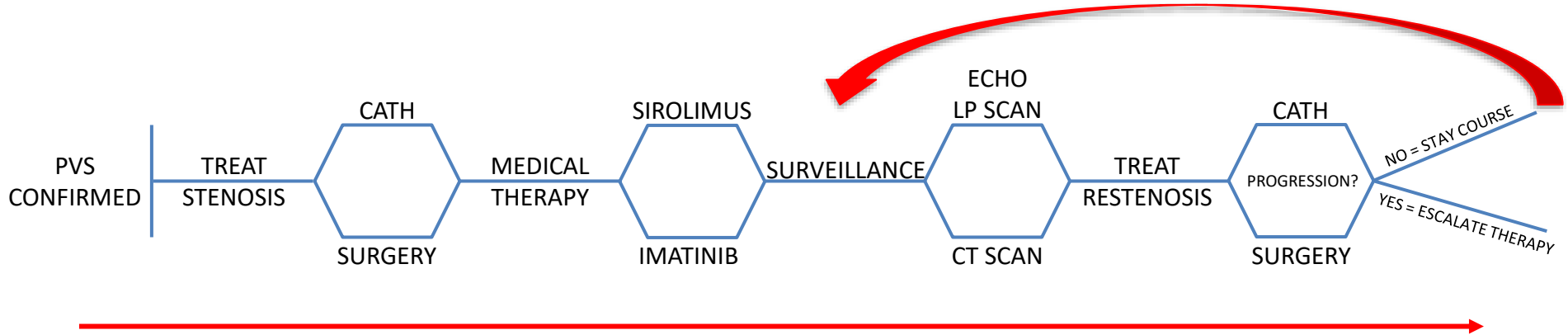
1. Diagnosis
2. Management

PVS Team



*Assertive and detail oriented

Standardize PVS Management



Diagnosis and Treat Restenosis Early

Multivariable Analysis of Serious Adverse Events at The Time of PVS Catheterization (n=841)

Multivariable Analysis of Serious Adverse Events	Odds Ratio	95% CI	P Value
Age at intervention <6 months 6-11.9 months ≥1 year	 2.05 1.30 1.00	 1.11, 3.81 0.77, 2.22 --	 0.023 0.33 --
Systemic arterial saturation <95% BiV, <78% SV	1.52	1.02, 2.27	0.041
Mean PA pressure ≥45 mm Hg BiV, ≥17 mm Hg SV	1.74	1.16, 2.63	0.008

Barreto JA et al. Pediatric Cardiology 2023.

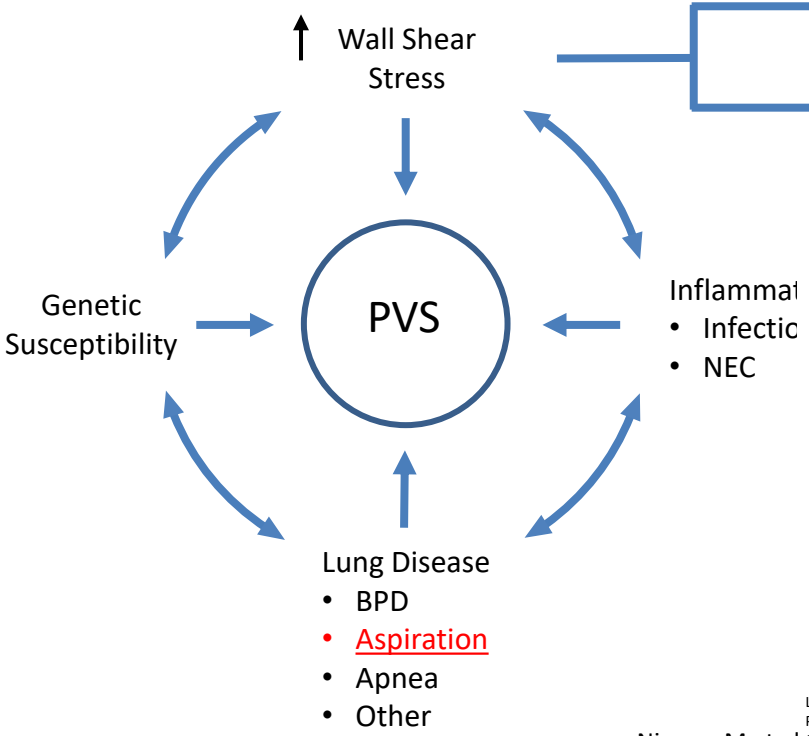
Table 5. Multivariate Analyses of Perioperative Factors and Postoperative ICU Admission and Mechanical Ventilation

N = 473

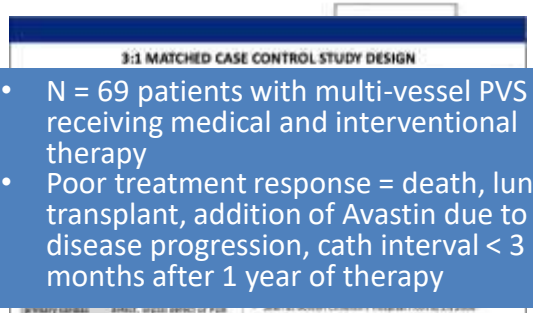
	ICU Admission		Mechanical Ventilation	
	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Male gender	3.93 (1.64-9.41)	0.002	2.89 (1.26-6.66)	0.013
Body weight,per 1 kg increment	0.80 (0.68-0.92)	0.003	0.79 (0.68-0.92)	0.002
Preoperative O_2 supplement	4.01 (1.69-9.53)	0.002	3.67 (1.55-8.68)	0.003
PVS severity score, per 1 unit increment	1.15 (1.02-1.30)	0.028	1.11 (0.98-1.24)	0.10
Hypotension requiring inotrope	4.03 (1.38-11.77)	0.011	2.89 (1.08-7.77)	0.035
Red blood cell transfusion	3.25 (1.18-8.94)	0.023	4.09 (1.53-10.93)	0.005
Preintervention PaO_2/F_IO_2 ratio, per 100 units increment	0.63 (0.45-0.89)	0.009	0.59 (0.42-0.83)	0.002
Preintervention RVSP, per 10 mmHg increment	1.39 (1.11-1.75)	0.004	1.27 (1.03-1.57)	0.023

Maisat W et al. J Cardiothorac Vasc Anesth 2022.

Remove PVS Triggers



Niccum M et al. Children 2021.



- N = 69 patients with multi-vessel PVS receiving medical and interventional therapy
- Poor treatment response = death, lung transplant, addition of Avastin due to disease progression, cath interval < 3 months after 1 year of therapy

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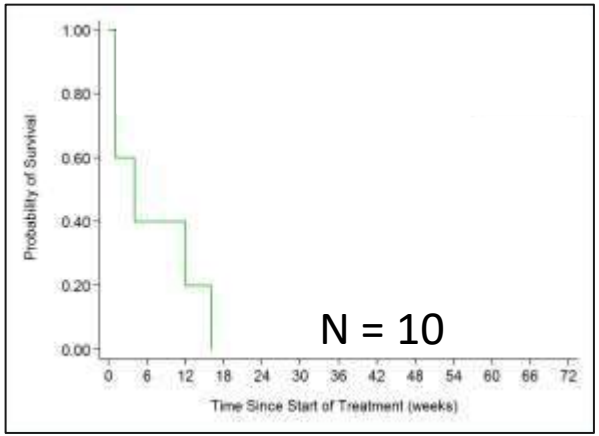
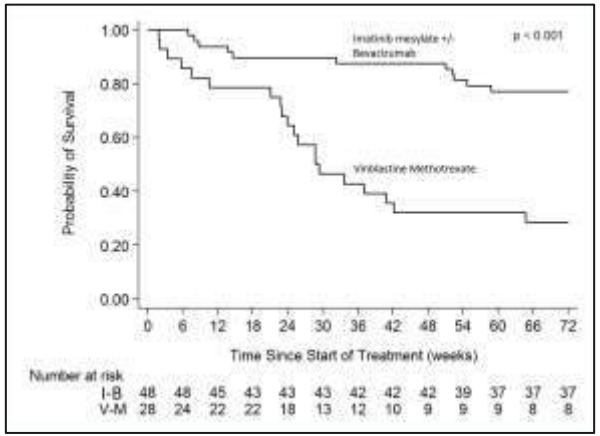
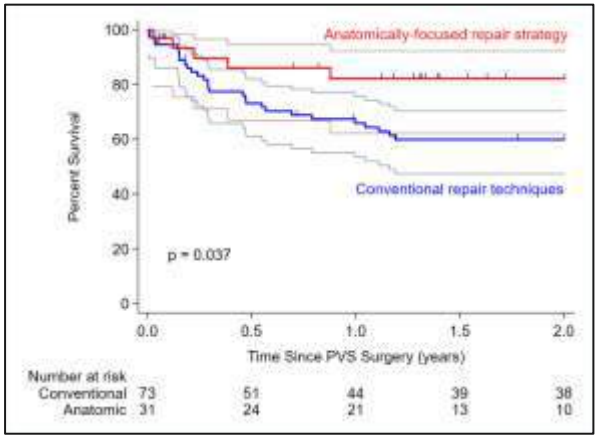
Longer Exposure to Left-to-Right Shunts Is a Risk Factor for Pulmonary Vein Stenosis in Patients with Trisomy 21. McArthur E et al. *The Journal of Pediatrics* 2024.

Lung Disease 3:1 case control trial from pool of 10171 patients. .38

Survival (Center 1)

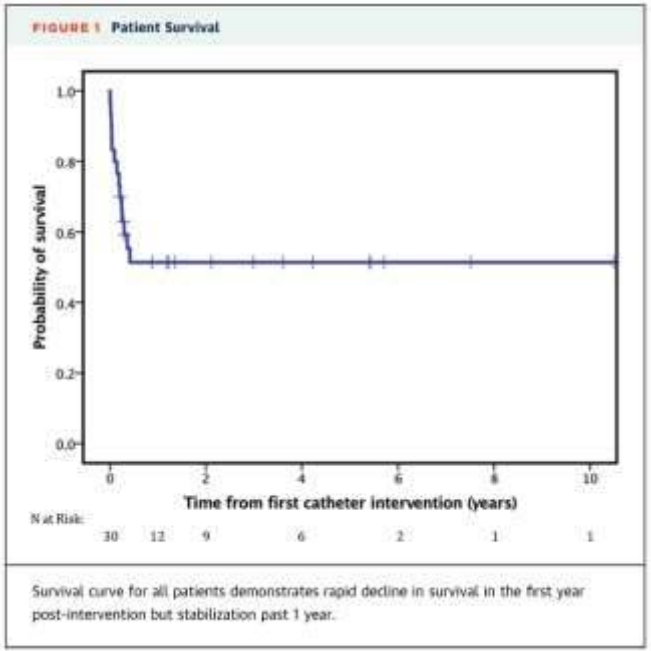




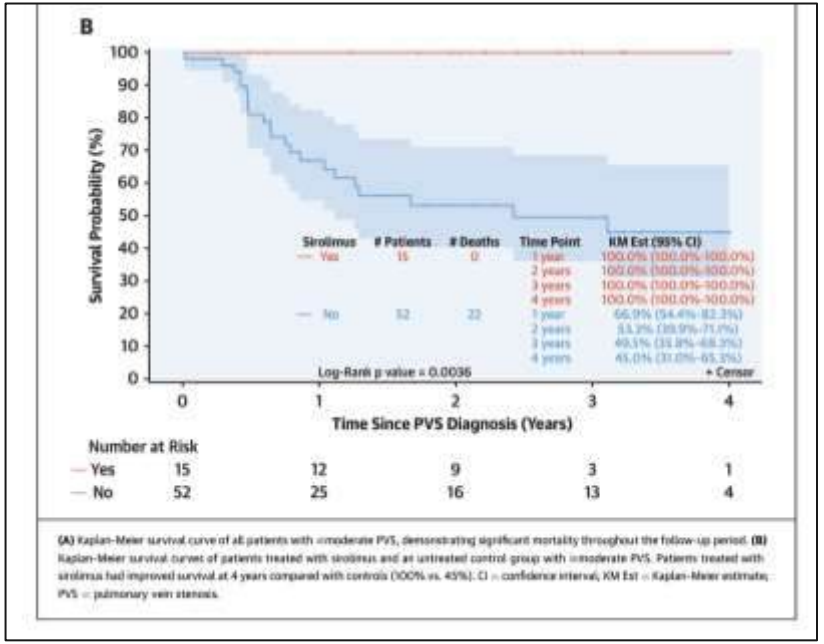


Sadr IM et al. *The American Journal of Cardiology* 2000.
Rehman M et al. *Congenital Heart Disease 2011.*
Callahan R et al. *The Journal of Pediatrics* 2018.
Feins EN et al. *The Journal of Thoracic and Cardiovascular Surgery 2021.*

Survival Outcomes (Center 2)



Cory MJ et al. *JACC: Cardiovascular Interventions 2017.*



Patel JD et al. *Journal of the American College of Cardiology* 2021.

Survival Outcomes (Center 3)

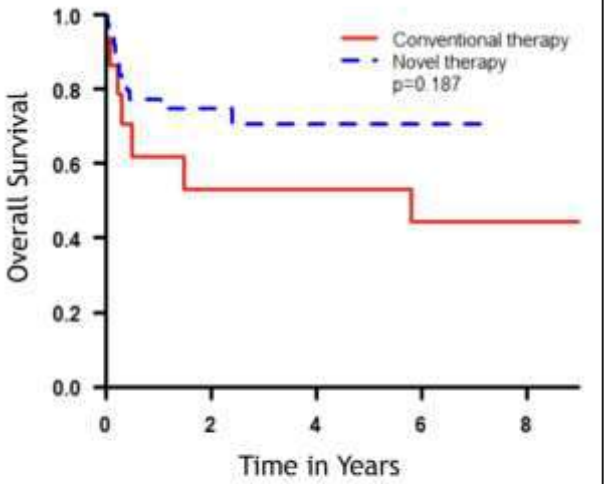
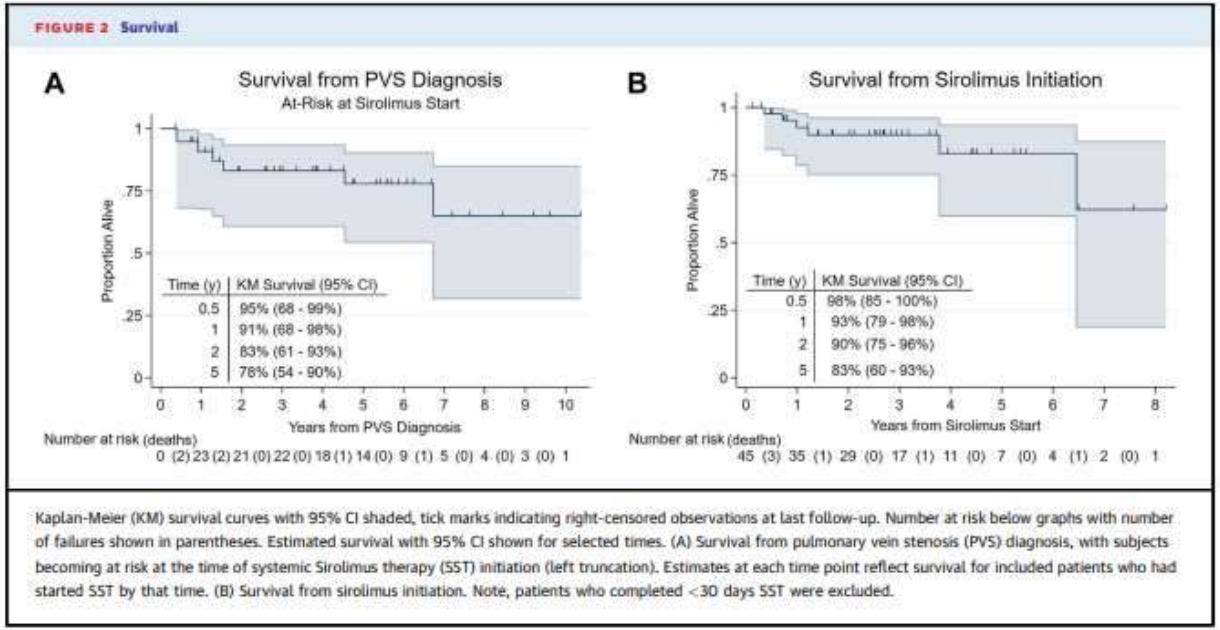


FIGURE 3 Survival curve comparing patients receiving conventional therapy using BMS alone (red) and novel therapy using a combination of DES and BMS (blue). BMS, bare metal stents; DES, drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

Khan A et al. *Catheter Cardiovasc Interv 2019.*



Kaplan-Meier (KM) survival curves with 95% CI shaded, tick marks indicating right-censored observations at last follow-up. Number at risk below graphs with number of failures shown in parentheses. Estimated survival with 95% CI shown for selected times. (A) Survival from pulmonary vein stenosis (PVS) diagnosis, with subjects becoming at risk at the time of systemic Sirolimus therapy (SST) initiation (left truncation). Estimates at each time point reflect survival for included patients who had started SST by that time. (B) Survival from sirolimus initiation. Note, patients who completed <30 days SST were excluded.

Kalustian AB et al. *JACC Adv 2024.*

How can we do better?

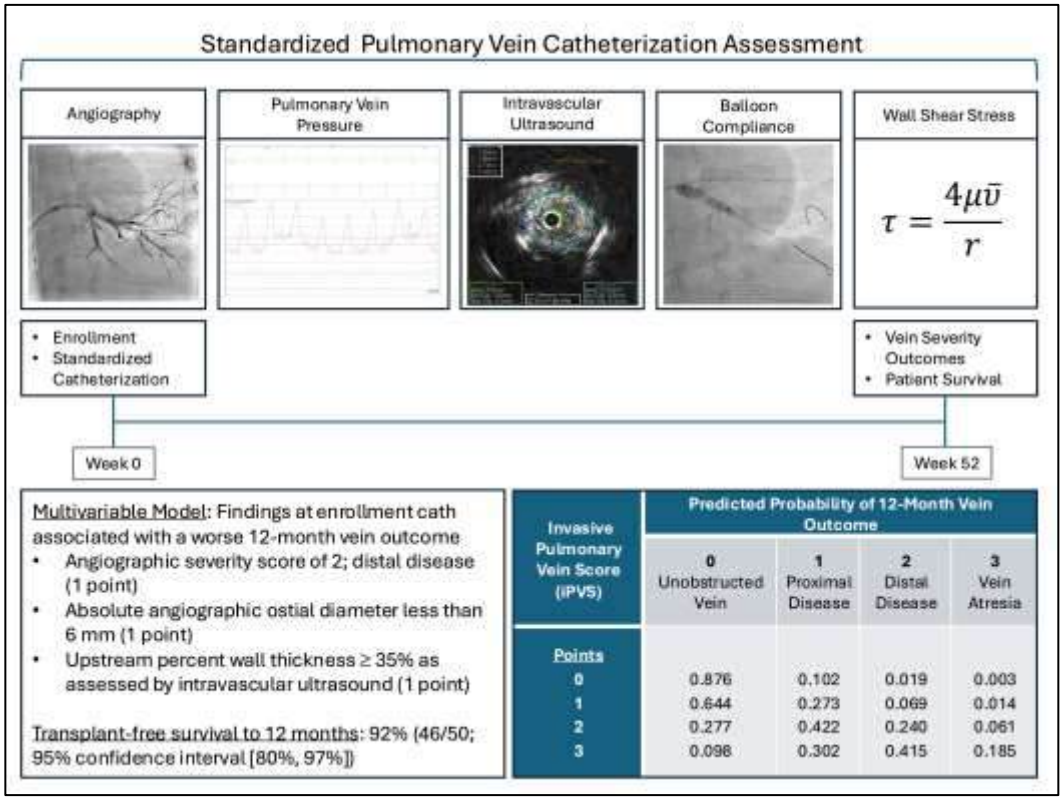
PVS Overall 5-year survival = ~70-80%

1. Optimize current therapies
2. PVS prevention
3. Novel therapies

Optimize Current Therapies

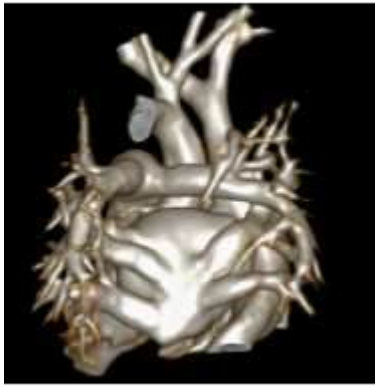
- Patient level
  - Multi-center PVS registry via Congenital Cardiac Research Collaborative
    - Identify best practices
    - Data acquisition begins 2025

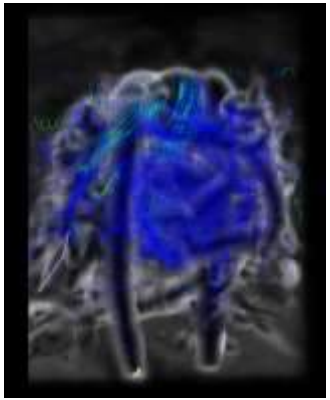
- Vein level
  - Multi-center Prospective Standardized Pulmonary Vein Catheterization Assessment (NCT 04696289)
    - Prediction Model Cohort
      - BCH: 50/50 enrolled
      - Under peer review
    - Validation Cohort
      - CHOP: 30/30 enrolled
      - Awaiting outcomes data



Prevention

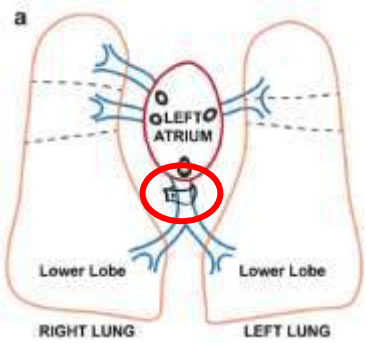
- Goal: Non-invasively ID high-risk infants for PVS; improve stratification
- Study: Calculate wall shear stress in pulmonary veins of infants using cardiac MRI, 4D flow and computational fluid dynamics
  - Quantify effect of removal of triggers
  - Known PVS: Prioritize pulmonary vein interventions which minimize WSS

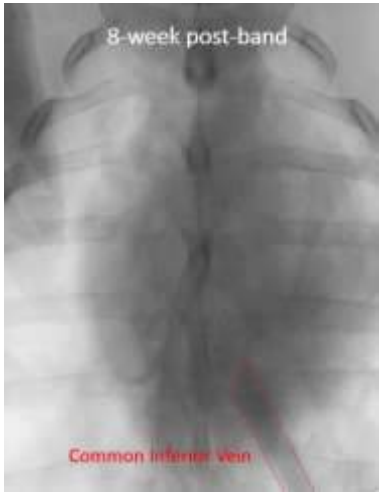




Novel Therapies

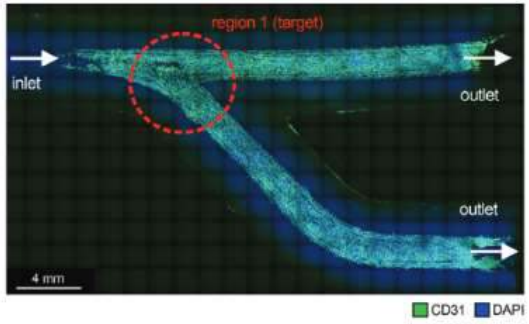
- Porcine PVS Model
  - scRNA sequencing
    - ID new targets for meds
  - Test new to market drug coated balloons
  - Test novel surgical techniques

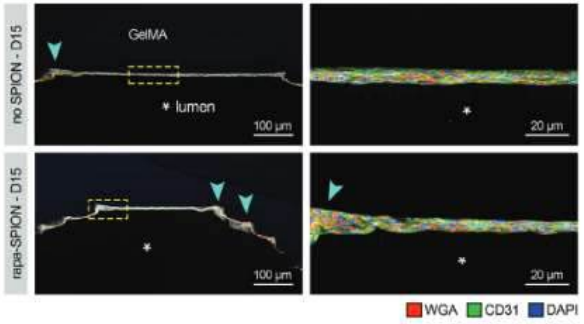




- Targeted rapamycin delivery via magnetic nanoparticles in an in vitro model of pulmonary veins

Ning L et al. Adv Sci 2024.





SUMMARY

- Early diagnosis, screening high-risk infants and management (therapy, surveillance, etc.) protocols have increased patient survival.
- Identifying best practices, optimizing current therapies, and knowledge sharing can further improve PVS outcomes.
- PVS prevention and novel therapies are needed to win the war.

PVS Team

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Kim Butler
Jihee Lee
Stephanie Fuller
Jack Rome
Kate Avitabile
Michael O'Byrne
David Frank
Mudit Gupta
Jess Tang
Dave Biko

PVS at CHOP

Save The Date

Pulmonary Vein Stenosis Symposium

Friday, April 4 and
Saturday, April 5, 2025

Hosted by

Children's Hospital of Philadelphia
Breakthroughs. Every day.

Roberts Center for Pediatric Research

REGISTRATION

Perelman School of Medicine
University of Pennsylvania