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PULMONARY ARTERY STENOSIS: EARLY INTERVENTIONS WITH LOW PROFILE STENTS VERSUS DELAYED INTERVENTIONS WITH LARGE DIAMETER STENTS

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ABSTRACT

Pulmonary artery stenosis (PAS) is a common complication of heart surgery in infancy. With recent advances in low profile-small diameter stent technology, PA stenting is now often performed in infants. While PAS stenting in older children does not impact distal PA growth and multiplication, in infants still undergoing significant PA growth, the impact of PA stent timing on long term PA development is unknown and potentially important. In a swine PAS model, the effects of early and delayed stent interventions on PA growth and cardiac function were comprehensively assessed. PA stenting had a positive impact on hemodynamics, lung perfusion, and histology, but the timing of intervention, either early or late, does not make a significant difference.

Keywords: pediatrics, pulmonary artery stenting

NOMENCLATURE

BSA	body surface area
bSSFP	balanced steady state free precession
CI	cardiac index
CO	cardiac output
CT	computed tomography
DI	delayed intervention
EI	early intervention
EDV	end diastolic volume
EF	ejection fraction
ESV	end systolic volume
IVS	interventricular septum
KE	kinetic energy
LV	left ventricle
mmHg	millimeter mercury
MRI	magnetic resonance imaging
PA	pulmonary artery
PAS	pulmonary artery stenosis
PCWP	pulmonary capillary wedge pressure
RA	right atria
RV	right ventricle
SV	Stroke volume
ε	energy dissipation
μ	viscosity
ρ	density
ω	vorticity

INTRODUCTION

Most children with complex forms of congenital heart disease (CHD) require corrective surgery during the first year of life [1] and although survival following these early repairs has improved dramatically, re-interventions are often necessary. Branch pulmonary artery (PA) stenosis is often the indication for re-intervention [2]. Acute post-surgical PA stenosis (PAS) may cause hemodynamic instability, prolonged in-hospital recovery and increased post-operative mortality. PAS also alters the critical early life period for lungs parenchyma and PA growth, where in a healthy individual there is rapid increase in alveoli number and concurrent expansion of the pulmonary vasculature from birth until 3-5 years of age [3], [4]. As a result of altered lung and PA growth, chronic PAS is associated with abnormal PA growth, PA hypertension and pulmonary valve insufficiency [5], contributing to chronic morbidity and mortality [6]. Animal models of PAS show abnormalities in PA growth, right ventricular (RV) function, lung parenchyma growth and lung function [7]. It would be ideal to treat PAS is early in life, preventing the long-term detrimental consequences. Surgical repair of PAS in infants and small children is frequently unsuccessful [8] so PAS is increasingly managed with catheter based stent interventions. PA stenting has been shown to be superior to surgery [9] but PA catheter interventions early in life have limitations and associated risks [10]. The optimal timing for intervention to minimize

complications and maximize normal lung development and PA growth remains unclear.

Given the critical importance of normal pulsatile pulmonary blood flow for PA development it is assumed that interventions performed earlier during the developmental phase would be superior to interventions performed later, when PA multiplication is no longer possible. Prior studies have documented the acute [11] and chronic [7] effects of early PA interventions in animal models however, no published studies compare outcomes of early versus delayed intervention for PAS, highlighting a significant gap in our knowledge. With the development of new stent technologies with low profile delivery systems and capabilities for expansion from small implant diameters to adult size, catheter interventions are now being performed in smaller children without knowledge of ultimate consequences. There is a critical need to understand the impact of timing of intervention for PAS on eventual PA development. This project defines the anatomic and physiologic consequences of untreated moderate PAS in a swine model [7] and compares lung and PA development and growth as well as hemodynamics and cardiac function following early and delayed catheter interventions. Our hypothesis is that an early stent intervention will lead to improved PA development and cardiac function compared to a delayed intervention.

MATERIALS AND METHODS

18 male swine were assigned to four groups: sham (n=4), untreated left PAS (LPAS, n=4), delayed intervention (DI, n=5) and early intervention (EI, n=5). LPAS, DI and EI had proximal LPAS created at 2 weeks age (5±1 kg). DI had stenting at 10 weeks (32±9 kg) with 10-12mm diameter stents (EV3 1610 DS). EI had LPA stenting at 5 weeks (5±1 kg) with low profile 6-7mm diameter stents (Valeo) and stent dilation at 10 weeks. The aim of the 10 week catheterization was to dilate the LPA stent to match the distal LPA diameter. All groups underwent right heart catheterization with dobutamine perfusion, CT, MRI and histology at 20 weeks (55±9 kg). The Institutional Animal Care and Use Committee of the University of Wisconsin reviewed and approved this protocol. The experimental timeline is shown in Figure 1.

PA diameters were measured from CT angiograms at the proximal LPA (stenosis/stent location), the LPA/RPA and the LPA/RPA first-order branches at consistently identified locations. PA dimensions are normalized to the aorta diameter measured at the diaphragm.

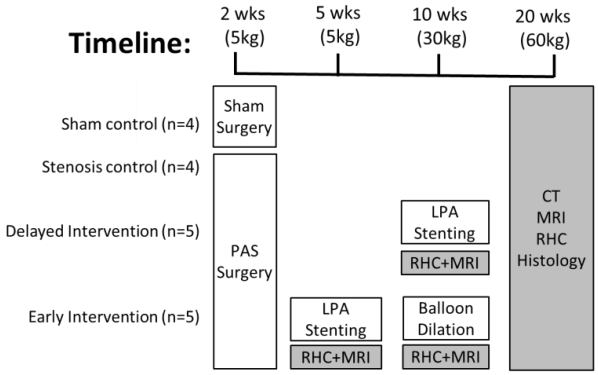

FIGURE 1: Experimental timeline showing delayed and early intervention sequences

From a balanced steady state free precesion (bSSFP) MRI sequence, short axis images are segmented to calculated end systolic and end diastolic ventricular volumes (ESV and EDV respectively), ejection fraction (EF) and cardiac output (CO). All ventricular volumes are normalized to body surface area (BSA) which is calculated from bodyweight. Cardiac index (CI) is CO normalized by BSA.

Lung perfusion is quantified using four dimensional flow sensitive MRI (4D Flow MRI), a technique that measures the three components of blood flow velocity within a volume.

4D Flow MRI is also used to analyze ventricular flow dynamics. Kinetic energy (KE), vorticity ($\boldsymbol{\omega}$) and energy dissipation rate (ε) are calculated from the following equations

$$KE = \frac{1}{2}\rho \boldsymbol{u}^2 \quad (1)$$

$$\boldsymbol{\omega} = \boldsymbol{\nabla} \times \boldsymbol{u} \quad (2)$$

$$\varepsilon = 2\mu(\boldsymbol{S})^2 \quad (3)$$

where ρ is blood density, $\boldsymbol{\nabla} \times$ is curl, μ is blood viscosity and $\boldsymbol{S}$ is the strain rate tensor. Results are non-dimensionalized to account for variance in CO and ventricle size.

Data are reported as mean ± standard error. In normally distributed data, statistical comparisons between groups were made by ANOVA with Tukey's honestly significant difference procedure used for post hoc comparisons. When data were not normally distributed, comparisons were made using the non-parametric Kruskal-Wallis test.

RESULTS

EI and DI restored LPA pulsatility and had normal RV pressure at baseline and with dobutamine perfusion (Table 1). Pressure gradients across stents were insignificantly higher for EI versus DI ($p = 0.14$). EI and DI improved, but did not normalize, left lung perfusion. EI and DI both trended towards increased CI, smaller RV volumes and increased RV EF compared to sham and LPAS. No differences were found for RV mass (RV/LV+IVS).

For EI and DI, the stent and LPA adjacent to the stent did not reach normal size but were larger than LPAS (Figure 2). Distal LPA and LPA branches were similar for sham, EI and DI but larger than LPAS. No differences were found for RPA and RPA branch diameters.

Time curves of non-dimensional KE, vorticity and energy dissipation rate are shown along with systolic and diastolic peak KE, average vorticity and average energy dissipation rate in Figure 3. LPAS trended towards higher KE, vorticity and energy dissipation rate in both ventricles. No differences between EI, DI and sham were found.

From histology there was a trend towards increased medial wall thickness in small arteries of the left lung in LPAS. Bronchial artery infiltration of the left lung was increased in LPAS compared to EI and DI, and was absent in sham controls. No differences were found for alveolar counts.

Table 1: Right heart catheterization hemodynamics and cardiac MRI

	Sham (n=4)	LPAS (n=4)	DI (n=5)	EI (n=5)
Body weight (kg)	56±3	57±2	59±3	48±5
Heart rate (BPM)	84±4	83±2	105±6	96±8
RV/LV+IVS (g/g)	0.42±0.02	0.40±0.02	0.41±0.02	0.44±0.02
Mean RA Pressure (mmHg)	7±2	10±1	6±1$^{\#}$	6±1$^{\#}$
RV Pressure (mmHg)	28±3 / 7±2	38±3* / 10±1	27±2$^{\#}$ / 7±1	29±1$^{\#}$ / 6±0
MPA Pressure (mmHg)	29±2 / 14±2	38±3* / 17±2	25±1$^{\#}$ / 13±0	28±1$^{\#}$ / 13±2
RPA Pressure (mmHg)	27±2 / 15±2	37±2* / 18±2	25±2$^{\#}$ / 14±1	24±2$^{\#}$ / 13±1
LPA Pressure (mmHg)	28±1 / 17±1	15±4* / 13±4	23±2$^{\#}$ / 14±1	22±2 / 13±2
Stenosis/Stent Pressure Gradient (mmHg)	1±2	23±3*****	1±1$^{\#}$	6±1$^{\#}$
PCWP (mmHg)	10±1	11±3	8±1	7±1
RV Pressure with Dobutamine (mmHg)	36±5 / 6±2	56±4* / 9±1	33±2$^{\#}$ / 6±0	39±3$^{\#}$ / 6±1
CI (L/min/m^2)	2.8±0.2	3.2±0.1	3.7±0.4	3.6±0.3
RV EDV/BSA (mL/m^2)	83±7	98±10	67±5	76±8
RV ESV/BSA (mL/m^2)	50±6	62±8	32±2$^{\#}$	38±6$^{\#}$
RV SV/BSA (mL/m^2)	33±3	36±2	35±4	38±4
RV EF (%)	40±3	37±3	51±3	51±4
Left lung perfusion (%)	52±5	7±2*	44±3$^{\#}$	40±2$^{\#}$

***** p<0.05 vs sham control, $^{\#}$ p<0.05 vs LPAS control

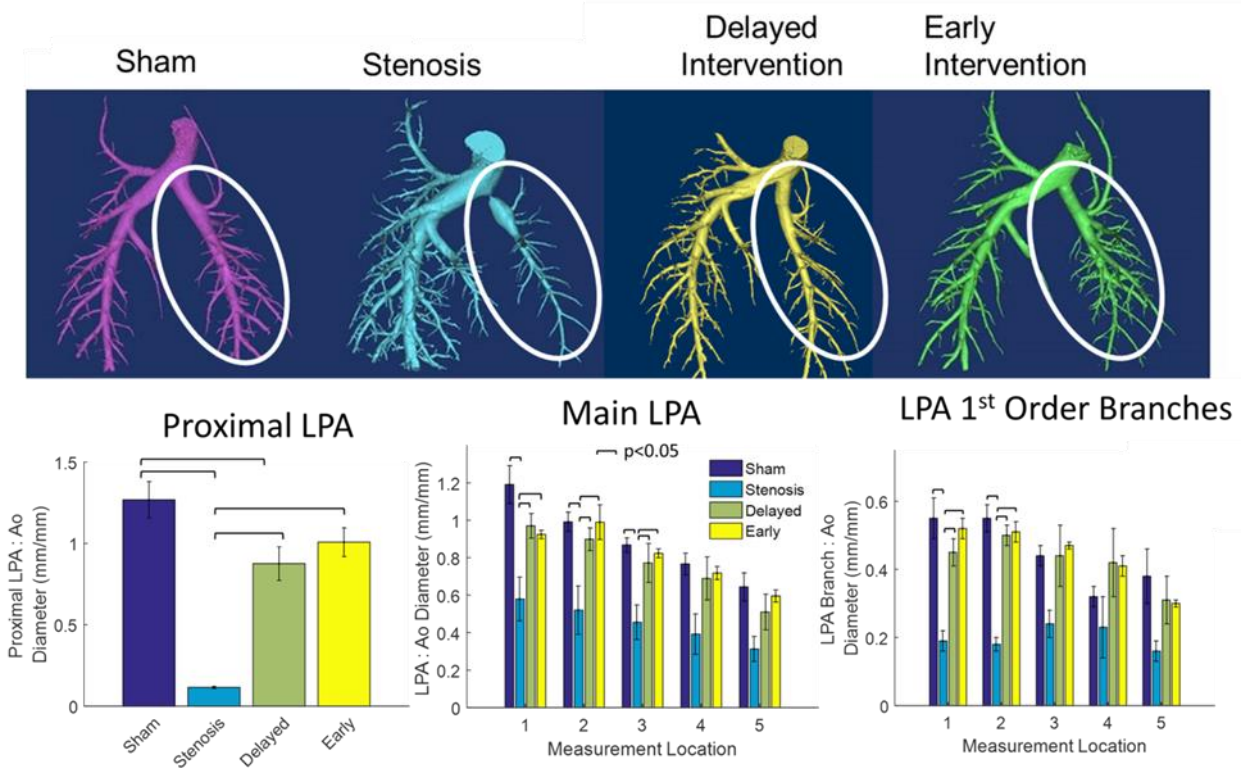

FIGURE 2: 3D reconstructions of PA anatomy show small LPA and branches distal to the stenosis. Intervention appears to normalize anatomy. Proximal LPA diameters show that EI and DI improve but do not normalize stenosis diameter. Adjacent to the stent (measurement location 1) LPA growth is impaired but more distal LPA and LPA branch diameters are normalized by intervention.

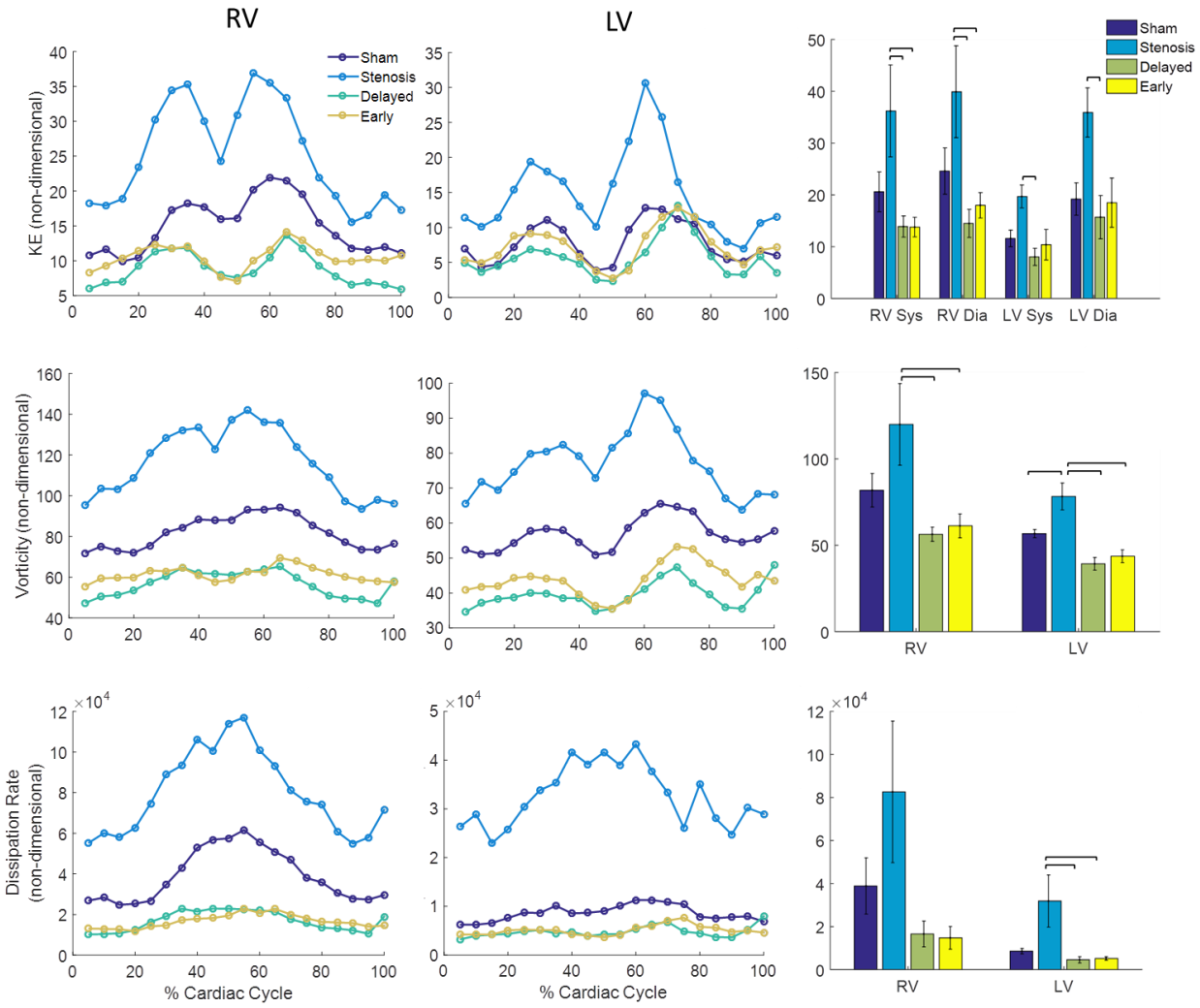

Figure 3: Time curves and bar graphs of non-dimensional flow parameters show the LPAS group has abnormal flow in both the RV and the LV. Standard error is not shown on the time curve plots. Row 1: kinetic energy, Row 2: vorticity, Row 3: energy dissipation rate.

DISCUSSION

The main aim of this study was to assess the effects of early and delayed catheter interventions on pulmonary vascular growth and cardiac function in a swine model of branch PAS. We found stent interventions to be effective for improving PA growth and cardiac function but intervention timing did not affect outcomes.

Pulsatile blood flow to the lungs is an important stimulus for driving growth and multiplication of the pulmonary vasculature and respiratory structures. As PA and alveolar multiplication is only possible early in life the ideal option for PAS management would restore normal pulmonary blood flow and reduce RV afterload as early in life as possible. A previous clinical study of 39 children showed that PAS patients with lower weight at the time of stent implantation showed greater lobar growth but the study did not include infants and 37/39 patients received large diameter stents [12]. This study is the first direct comparison between early interventions with low profile-small diameter stents and delayed interventions with large diameter stents.

PA stent interventions do not normalize the stenotic site size. The stented region has no potential for somatic growth and at 10 weeks the stent can only be expanded to the current size of distal PA to minimize the risk of vessel dissection. The PA immediately distal to the stent also does not grow normally due to interactions with the stented region [13]. Perfusion of stented lungs is still 10% lower than sham controls and both DI and EI have abnormal histopathology.

Consistent with our prior swine study, CI is elevated in intervention groups [7]. Along with elevated RV EF, this data suggests that in early life the RV adapts to pump against increased afterload and that increased RV function is retained at least until our end study time point. While these results seem at odd with exercise intolerance in PAS patients, elevated CI could be due to impaired gas exchange and respiratory function. Although alveoli counts from histology were not found to be different but we did not measure respiratory

function as standard lung functional measurements are difficult in swine. Novel non-invasive imaging techniques of lung function could be employed in future large animal studies of PAS.

Ventricular flow analysis using 4D Flow MRI is an increasing utilized method for studying ventricular function. Studies have shown KE and vorticity to be altered in a variety of cardiovascular diseases. A recent study showed that ventricular flow assessed with 4D Flow MRI independently predicted 6 minute walk test while EF, LV volumes and biochemical markers of cardiac remodeling did not [14]. In our current study the LPAS group had mildly increased RV pressures which matches clinical PAS symptoms [7], [8]. The PAS group had abnormal and inefficient flow in both the RV and the LV despite normal HR, CI and EF values and only the RV being directly affected by the stenosis. The detection of altered RV and LV flow with only mild pulmonary hypertension underscores the sensitivity of 4D Flow MRI derived biomarkers to detect cardiac dysfunction.

A key limitation of the swine PAS model is that the experimental time course is short compared to humans where PA stents are present for years. The amount of scar tissue development, in-stent stenosis and their subsequent effects on PA growth could be underestimated. This study also only used male swine and cardiovascular sex differences are known to be important.

CONCLUSION

In this swine PAS model, early interventions are not more effective than delayed interventions. While catheter interventions have clear benefits for PA growth, persistent functional and anatomical discrepancies between intervention groups and sham controls exist. These differences include impaired PA growth adjacent to the stent and abnormal lung histopathology.

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