Global healthcare disparities and new technologies: the rule of 3D cardiac printing in managing a child with severe pulmonary arterial hypertension

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Introduction: Global healthcare disparities can result in limited healthcare access for children with undiagnosed congenital heart disease (CHD) resulting in pulmonary arterial hypertension (PAH). Once these children get healthcare access and are diagnosed with PAH, healthcare providers encounter challenging treatment dilemmas. We present a child with severe PAH secondary to untreated unrestricted ventricular septal defect (VSD), who was successfully treated with Treprostinil, Tadalafil, and Ambrisentan and referred for surgical repair.

Case description: An 11-year-old previously healthy girl was referred to cardiology for evaluation of a murmur and evidence of failure to thrive. She had recently immigrated to the United States. She reported exercise intolerance, but no history of cyanosis, shortness of breath at rest, chest pain, palpitations, pre-syncope, or syncope. Her exam demonstrated a loud S2 and II/VI systolic murmur at the left lower sternal border with no evidence of clubbing or cyanosis. ECG showed evidence of right ventricular hypertrophy (RVH). Her initial echo showed a PFO with bidirectional shunting, a large muscular VSD with bidirectional shunting, and moderate dilatation and hypertrophy of the RV. PAH treatment was initiated and three cardiac catheterizations were performed. At the last catheterization, the patient was deemed to be a candidate for percutaneous VSD closure. Subsequently, the patient underwent a cardiac CT. Heart model was 3D printed. The model showed the proximity of the VSD to the tricuspid valve, which precluded device closure; therefore, she was referred for surgical repair.

Discussion: 3D printing is a rapidly expanding technology with diverse medical applications, with great potential in pediatric cardiology. This technology helped to guide our team to choose the best approach for this patient. Additionally, this case highlights the impact of healthcare disparities when dealing with vulnerable children with undiagnosed CHD.

Fibroblast growth factor signaling is protective in hypoxia-induced pulmonary hypertension

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Background: Group 3 pulmonary hypertension (PH) is caused by hypoxemia resulting from bronchopulmonary dysplasia (BPD). Fibroblast growth factor 2 (FGF2) and FGF receptor 1 and 2 (FGFR1/2) levels are elevated in PH patients. Additionally, FGF2 is elevated in premature infants with bronchopulmonary dysplasia (BPD) and in mice exposed to chronic hypoxia. We have shown that endothelial FGFR1/2 signaling is important for response to injury. We hypothesize that FGF2 and endothelial FGFR1/2 signaling promotes endothelial cell survival and elaboration of signals that protect against PH.

Methods: The Tie2-Cre transgene was used to conditionally regulate Fgfr1 and Fgfr2 expression in endothelial cells. We also generated an inducible constitutively active FGFR1 (caFGFR1). Mice with the genotypes Tie2-Cre;Fgfr1f/f;Fgfr2f/f (DCKO), Fgf2−/−, and Tie2-Cre;Rosa26RTTA;Tre-caFgfr1 were challenged with 10% hypoxia for two weeks, followed by cardiac catheterization to measure right ventricular pressure (RVP). We also engineered a microfluidic device to simulate physiologically relevant blood vessels.

Results: Compared to control littermates, DCKO mice in hypoxia developed worse RVP, increased RV hypertrophy, and decreased RV function, demonstrating worsening PH. Furthermore, mice with a global deletion of Fgf2 developed more severe PH than DCKO mice when challenged in hypoxia. Notably, mice with endothelial overexpression of caFGFR1 showed RVP similar to control mice in normoxia. In microfluidic devices, primary pulmonary endothelial cells from DCKO mice altered smooth muscle cell morphology resulting in extracellular matrix deformation.

Conclusions: We conclude that loss of endothelial FGFR1/2 worsens hypoxia-induced PH and RV function in vivo and alters...
smooth muscle cell physiology in vitro. Furthermore, FGF2 is important for the pathogenesis of Group 3 PH and acts at least in part through the endothelial FGFRI/2 pathway. We show that overexpression of constitutively active FGFRI in endothelial cells prevents hypoxia induced PH in vivo. Our data suggest that activation of endothelial FGF signaling protects against Group 3 PH, the opposite of what is reported in Group 1, and regulates endothelial to vascular smooth muscle cell interactions.

**A fetal finding of pulmonary hypertension with a filamin A (FLNA) variant**

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**Hypothesis:** We propose that the novel FLNA variant NM_001456 exon 8 p.Thr402Ala (c.1204A > G) is associated with severe primary pulmonary hypertension (PH). This has not been previously reported in the literature. Fetal echocardiogram with abnormal pulmonary venous flow patterns, right ventricular enlargement, and borderline left-sided structures may be suggestive of pulmonary venous bed abnormalities with severe primary PH at birth.

**Methods:** Fetal echocardiograms at 29 and 32 weeks. Postnatal echocardiograms. Cath lab.

**Results:** Fetal echocardiogram with abnormal pulmonary vein flow, borderline left-sided structures, right ventricular enlargement, and left-to-right shunting at the foramen ovale. Postnatal echocardiogram, borderline left-sided structures, obstructive pulmonary vein Doppler with normal peak velocities. Catheterization at 19 days of age: right ventricular pressure 100/12; pulmonary vein pressure 7–11 mmHg; left atrial mean pressure 8 mmHg; left ventricular pressure 52/12; pulmonary vascular resistance (PVR) 12 units/m². On 100% oxygen and 20 ppm nitric oxide PVR decreased to 7.2 units/m². Patient ultimately discharged home at six months of age on sildenafil and home ventilator.

**Conclusion:** In this patient with primary PH, there was no evidence of congenital heart disease to support the finding of PH. With the finding of this specific FLNA variant (c.1204A > G), it is the probable etiology for primary PH in this patient.

**Performance of the pediatric risk stratification model in children with pulmonary arterial hypertension**

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**Background:** Guidelines advise risk stratification models as tools for identifying patients with pulmonary arterial hypertension (PAH), at higher risk for adverse clinical outcome and allowing for optimizing treatment strategies and improving prognosis. In children with PAH, we investigated the value of the pediatric risk model proposed at the 2013 World Symposium on Pulmonary Hypertension (WSPH), augmented with risk determinants proposed for adults in the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, both at baseline and at one-year follow-up.

**Materials and Methods:** Children aged ≤ 18 years diagnosed with idiopathic or heritable PAH (PAH/HPAH) between 1993 and 2017 were included. Clinical, functional, echocardiographic, and hemodynamic characteristics were collected at time of diagnosis and one year after diagnosis. Outcome was defined as transplant-free survival.

**Results:** Fifty-eight patients were included for risk stratification at diagnosis and 44 for risk stratification at one-year follow-up. The median (interquartile range) age was 6.8 (2.2–13.4) years, 53.4% were female patients. Median follow-up duration was 3.1 (0.7–8.4) years. Both at baseline and at one-year follow-up the pediatric risk stratification model predicted transplant-free survival. At baseline, patients with ≥ 3 low-risk criteria had a better long-term prognosis than patients with ≤ 2 low-risk criteria. At diagnosis, children with five low-risk criteria at diagnosis had one-, three-, and five-year survival rates of 100%, 91%, and 80%, with three low-risk criteria: 73%, 73%, and 73% and with no low-risk criteria: 57%, 29%, and 14%, respectively. At follow-up, children with two low-risk criteria had one-, three-, and five-year survival rates of 100%, 100%, and 92%, whereas those with no low-risk criteria had 71%, 14%, and 14%, respectively. The pediatric risk model performed best at follow-up.

**Conclusion:** The “augmented” WSPH pediatric risk stratification model successfully predicts transplant-free survival in pediatric PAH patients, both at baseline and at one-year follow-up.

**In vivo skeletal muscle energetics during exercise in pulmonary arterial hypertension**

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**Background:** Patients with pulmonary arterial hypertension (PAH) typically present with exercise intolerance. Decreased skeletal muscle strength has also been reported in these patients. In addition to diminished cardiac output, additional factors such as intrinsic skeletal muscle abnormalities are reported. Here, in a pilot study, we investigated in vivo skeletal muscle energetics in response to exercise in children with PAH in comparison with healthy controls.

**Material and Methods:** Patients with PAH (n = 3) and healthy controls (n = 6) aged 8–18 years performed an intra-MRI maximal bicycling exercise test. First, patients performed a cardio-pulmonary exercise to assess exercise capacity and oxygen consumption. Two weeks later, dynamic Phosphorus Magnetic Resonance Spectroscopy (31 P-MRS) recordings of quadriceps muscle energy balance and pH were obtained during rest, exercise, and recovery. The following physiological endpoints were
determined for each individual: maximum workload; VO₂max; phosphocreatine (PCr) concentration (representing muscular energy reserve) and pH at end of exercise; and time constant of post-exercise PCr recovery.

**Results:** PAH patients show lower maximum workload (43–60%) and VO₂max (49–52%) compared to reference values. End-exercise PCr concentrations were higher (25.0 ± 6.30 vs. 12.9 ± 6.6 mM) in PAH patients and pH values of 6.97 ± 0.02 vs. 6.93 ± 0.14 compared to controls. Post-exercise metabolic recovery was not different in patients and controls (PCr time constant 30 ± 11 vs. 23 ± 6 s).

**Conclusions:** We demonstrate that high muscular energy reserves remain present at maximal exercise in PAH patients. These results suggest that lower exercise capacity observed in this PAH population is principally due to central, not peripheral, limitation.

**Sex-specific differences in clinical outcome and right ventricular adaptation to increased afterload during transition of rat pups into adolescence**

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**Background:** Outcome in patients with pulmonary arterial hypertension (PAH) is related to the degree and onset of clinical right ventricular (RV) failure due to increased RV afterload. Female PAH patients are known to have better RV adaptation and clinical outcome than male patients. It is unclear whether these sex-specific differences occur also in childhood, either before or after the onset of puberty. We therefore aim to compare clinical and hemodynamic features in response to increased RV afterload between male (M) and female (F) rats during transition from pre to post puberty.

**Materials and Methods:** Rat pups (30–45 g) were subjected to increased RV afterload by pulmonary artery banding (PAB) or sham surgery and studied from childhood into adolescence (PAB: 4 weeks M/F, n = 7/5; 8 weeks M/F, n = 10/5; Sham: 4 weeks M/F, n = 5/3; 8 weeks M/F, n = 5/3). Clinical symptoms of RV failure (bodyweight, dyspnea, pleural effusion/ascites) were collected and sequential echocardiograms were performed at four and eight weeks.

**Results:** The degree of pressure load (PL) was similar in male and female rats at four and eight weeks. At four weeks, male and female rats showed similar weight gain, equally reduced cardiac index, and tricuspid annular plane systolic excursion. After four weeks, coinciding with start of adolescence, male PAB rats showed reduced weight gain, and at eight weeks, more frequent clinical signs of RV failure and further deterioration of CI, when compared to female PAB rats.

**Conclusions:** This childhood rat model of fixed increased RV afterload, showed a better RV adaptation pattern in female than male rats, associated with better clinical outcome and preserved CI. These sex-specific differences occurred not before adolescence, suggesting hormone-driven mechanisms. This model provides clinical resemblance with human PAH and allows for further investigation of sex-specific differences in RV adaptation to increased afterload.

**Decrease of polyunsaturated fatty acids in right ventricular dysfunction due to pressure overload**

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**Background:** Right ventricular (RV) failure due to pressure load is an important determinant of clinical outcome in pulmonary hypertension (PH). Recently, changes in ventricular lipid content has been suggested as potential inducer of pediatric heart failure. In the present experimental rat study, we aimed to obtain insight in temporal changes in RV function, remodeling, and metabolism due to increased RV afterload, with specific focus on RV lipid content.

**Material and Methods:** Wistar rats were subjected to pulmonary artery banding (PAB; n = 25) or sham surgery (n = 14). Hemodynamic parameters were derived with echocardiography, whereas cellular and metabolic assessments took place using quantitative polymerase chain reaction (qPCR), stainings, and Oroboros at 2, 5, and 12 weeks. Lipidomic analysis was performed at 12 weeks of pressure load.

**Results:** In this model, early RV dysfunction and progressive RV remodeling occurred without clinical failure. After 12 weeks of pressure load, lipidomics revealed significant decreases of myocardial diglyceride and cardioliopin species; triglyceride also tended to be decreased. These decreases were driven by the downregulation of polyunsaturated fatty acids, including the abundant form tetratinoleolcardiolipin. Changes in intracardiac lipid profile were accompanied with an increase in carbohydrate metabolism without changes in mitochondrial fatty acid metabolism. This altered the balance between fatty acid carbohydrate metabolism in favor of the latter.

**Conclusions:** We conclude that RV dysfunction due to PAB is associated with decreased RV lipid content, characterized by a decrease of polyunsaturated lipids, including tetratinoleolcardiolipin, in the absence of clinical failure. The present study suggests that altered intra-cardiac lipid composition precedes and contributes to the development of RV failure.

**Pulmonary artery size is associated with functional status in the Fontan circulation**

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**Background:** In the Fontan circulation, non-pulsatile pulmonary blood flow has been suggested to negatively affect
pulmonary artery growth over time. The pulmonary vasculature is believed to be key determinant in outcome of the Fontan circulation. We hypothesized that, in Fontan patients, pulmonary arterial size correlates with follow-up and functional clinical status.

**Materials and Methods**: Single-center retrospective cohort study. Forty-two pediatric and adult Fontan patients, who had a concomitant cardiac magnetic resonance scan (CMR) and a cardiopulmonary exercise test (CPET) in 2012–2013 were included. Left and right pulmonary artery (LPA/RPA) cross-sectional areas (CSA) were measured using CMR and were expressed as Nakata index (CSA LPA + RPA / body surface area, mm²/m²). Functional status was defined as peak oxygen consumption (peakVO₂) indexed for weight (mL/min/kg) and as New York Heart Association Functional Class (NYHA-FC).

**Results**: Mean age at CMR was 17.6 (±7.0) years. Mean time between Fontan completion and CMR was 11.8 (±7.2) years. Mean time between CMR and CPET was 37 (±72) days. Mean Nakata index was 238.4 (±76.1) mm²/m², which is lower than normal reference values (330 ± 30 mm²/m²). Nakata index correlated negatively with both age at CMR (r = −0.378, P = 0.013) and time since Fontan completion (r = −0.330, P = 0.033). Mean peakVO₂ was 27.4 (±8.3) mL/min/kg and 54 (±14) % of predicted. Nakata index correlated positively with both peakVO₂ indexed for weight (r = 0.500, P = 0.001) and as percentage of predicted (r = 0.355, P = 0.021). Nakata index correlated negatively with NYHA-FC (r = −0.426, P = 0.005).

**Conclusions**: Pulmonary artery size expressed as Nakata index is lower in older Fontan patients. A higher Nakata index correlated significantly with a better functional clinical status defined as NYHA-FC and peak oxygen consumption. Chronic abnormal non-pulsatile pulmonary blood flow in Fontan circulation could play a detrimental role in this phenomenon.

**Prevalence and risk factors for pulmonary hypertension in preterm infants with bronchopulmonary dysplasia: a prospective study**

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**Background**: Neonatal care has drastically improved, resulting in survival of extremely premature babies and increased incidence of bronchopulmonary dysplasia (BPD) associated co-morbidities. Among that, pulmonary hypertension (BPD-PH) has high mortality and morbidity. The diagnosis of BPD-PH is difficult since the symptoms overlap with severe BPD. Cardiac catheterization is a highly invasive gold standard procedure for diagnosing PH. Our hypothesis was that unique inflammatory biomarkers in tracheal aspirates from preterm babies are associated with BPD-PH. These biomarkers may reflect underlying inflammatory pathways involved in development of BPD-PH.

**Methods**: We collected tracheal aspirates from a small cohort of infants at the Penn State Children’s Hospital NICU. Patients with confirmed clinical diagnosis based on NHLBI classification of severe BPD (n = 6), BPD-PH (as diagnosed based on echocardiogram findings) (n = 6), and term control babies (n = 5) were enrolled for the study. Samples were digested; iTRAQ labeled and analyzed via mass spectrometry using ABSciex 5600 Triple TOF and protein identification was accomplished using ProteinPilotTM4.5Beta software. Significantly different proteins in the groups were analyzed with Ingenuity Pathway Analysis (IPA) software (Qiagen).

**Results**: Over 700 different proteins were identified using Proteinpilot software. Applying very stringent local false discovery rate estimation, approximately 200–330 proteins were confidently identified in each sample. Twenty-two proteins and 16 proteins were significantly differentially (under or over) expressed when comparing control vs. BPD group and control vs. BPD-PH groups, respectively. Four proteins were common in these two datasets, but they differentially expressed namely lysozyme C precursor, lactotransferrin isofrom 1 precursor, polymeric immunoglobulin receptor precursor, and mucin-5B precursor (MUC-5B); MUC-5B precursor had the most statistically significant differential log ratio expression. IPA analysis of these four proteins showed relevant pathways between NFKB (complex), RELA, CDKN1A, TNF, TP53, and PRKCD.

**Conclusion**: Our pilot project revealed four proteins whose expression was significantly different in severe BPD vs. BPD-PH; IPA analysis predicted specific underlying inflammatory pathways. Further investigation into these proteins is warranted to explore potential for biomarkers for early diagnosis and target therapies.
Results: Of 126 infants enrolled (mean birth weight [BW] 858 ± 221 g; mean GA 26.1 ± 1.6 weeks), 48 infants (38%) developed PH at any time during their hospital stay. The prevalence of PH was 36/126 (28.5%) at enrollment, at 5/17 (29.4%) at 32 weeks, 24/111 (21.6%) at 36 weeks, and 11/63 (17.4%) at 40 weeks. No new cases of PH were identified at 40 weeks. At 36 weeks, none of the infants with mild BPD had PH, whereas 20% of moderate and 32% of severe BPD infants had PH. Infants with PH had lower BW and GA. After controlling for confounding variables (GA, antenatal steroids, illness severity score), severe BPD (odds ratio [OR] 3.73, 95% confidence interval [CI] 1.26–11) and ventilator-associated pneumonia (VAP) (OR 4.5, 95% CI 1.14–17.7) remained independent risk factors for PH.

Conclusion: Echocardiographic screening for PH can be safely restricted to infants with moderate or severe BPD at 36 weeks, none of the infants with mild BPD had PH, whereas 20% of moderate and 32% of severe BPD infants had PH. Infants with PH had lower BW and GA. After controlling for confounding variables (GA, antenatal steroids, illness severity score), severe BPD (odds ratio [OR] 3.73, 95% confidence interval [CI] 1.26–11) and ventilator-associated pneumonia (VAP) (OR 4.5, 95% CI 1.14–17.7) remained independent risk factors for PH.

Recanalization of the ductal origin of a discontinuous right pulmonary artery leading to reperfusion injury and severe pulmonary hypertension

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Background: Ductal origin of a discontinuous pulmonary artery is rare in the pediatric population. Catheter recanalization is attempted to rehabilitate perfusion and growth to the disconnected pulmonary arterial system but can lead to reperfusion injury and elevated pulmonary pressures.

Case description: The patient presented as a three-month-old, former 28-week gestation infant with bronchopulmonary dysplasia (BPD) and pulmonary hypertension (PH) thought to be secondary to her lung disease on oral sildenafil. In the early neonatal period before transfer to our institution, she was evaluated by cardiology and found to have ductal origin of her right pulmonary artery not amenable to therapy. She was transferred to our institution for further management. Angiography demonstrated appropriate vasculature throughout the right lung. The baseline mean pulmonary arterial (PA) pressure was 30 mmHg with a pulmonary vascular resistance (PVR) at 7.26 Wood units (WU). Recanalization of the right ductus communication to the anomalous right PA was completed. Reperfusion injury resulted after the procedure with progressive suprasystemic PH and severe right ventricular (RV) dysfunction. She was quickly escalated to maximal medical management including vasoactive and enteral, inhaled and parenteral PH therapies. She returned to the cardiac catheterization lab and was found to have suprasystemic RV pressure with PVR of 28.5 WU. The ductal stent was occluded at this time in hopes of reducing her pulmonary pressures. After two months of intensive medical management, she underwent surgical repair of her pulmonary arteries. She was weaned off of continuous prostacyclin therapy and remains on sildenafil and bosentan.

Discussion: Recanalization of a pulmonary artery with ductal origin, though it may allow for growth of both the vascular and parenchymal pulmonary beds, may inadvertently lead to exacerbation of underlying PH. However, with aggressive management, this can be managed and ultimately a positive result can be obtained.

Clinical characteristics and risk factors for developing pulmonary hypertension in children with Down syndrome

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Background: Children with Down’s syndrome (DS) are at increased risk for developing pulmonary hypertension (PH); however, the incidence, characteristics, and associated risk factors are uncertain. The objectives of this study are to determine the incidence and characteristics of PH in children with DS and to identify contributing co-morbidities.

Materials and Methods: This is a retrospective review of a large cohort of children with DS (n = 1242) who receive care at a center that specializes in DS. Clinical data and serial echocardiograms were reviewed from a prospective patient clinic database and electronic medical records. Details surrounding PH characteristics and co-morbidities were reviewed and reported.

PH was considered transient if echocardiographic evidence of PH resolved without recurrence, persistent if no resolution, and recurrent if echocardiographic evidence of PH returned after a period of resolution.

Results: The incidence of PH in children with DS was 28% (n = 346). Median age at initial diagnosis was 5 days (range 0–7067 days), with 86% diagnosed by one year of age. PH was further differentiated into transient (70%), persistent (15%), and recurrent (15%) disease. Median duration of transient PH was 9.7 months (range 0.1–130.2 months). Median age at recurrence was 2.5 years (range 0.2–11.5 years). Initial PH diagnosis was classified as WHO Group I disease in 82% with 45% associated with congenital heart disease (CHD) and 38% persistent PH of the newborn (PPHN). A majority (87%) of patients with recurrent PH were classified as WHO Group III. Frequently identified co-morbid conditions included CHD (94%), obstructive sleep apnea (OSA; 78%), intermittent hypoxia (56%), and recurrent pneumonia (43%). For those with recurrent disease, respiratory co-morbidities were common.

Conclusions: PH is common in children with DS, is typically transient and related to CHD or PPHN but can recur in the setting of respiratory disease such as OSA, intermittent hypoxia, and recurrent pneumonia.
Stability of treprostinil with diluents and medications

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Background: The safety and efficacy of intravenous (IV) treprostinil in neonates with persistent pulmonary hypertension (PH) is currently being evaluated in a randomized, placebo-controlled, Phase II study (NCT02261883). Lack of data demonstrating stability of treprostinil with diluents and IV medications commonly used in this population complicates care due to line access issues.

Materials and Methods: Treprostinil was diluted in 5/10% dextrose in water (DS/D10W); diluted in normal saline (NS) and individually combined with 11 IV medications at lower and higher concentrations; and diluted in NS and combined with heparin at a single concentration. Samples were stored at ambient conditions (unless otherwise indicated) and assessed for stability over time. Physical stability was demonstrated by visual assessment (precipitation or color change) and chemical stability was evaluated by high-performance liquid chromatography.

Results: Three concentrations of treprostinil (0.00025, 0.004, 0.13 mg/mL) in DS/D10W were stable at 25°C/60% relative humidity to 54 h. Lower-concentration treprostinil (0.4 mg/mL) with dopamine (1.6 mg/mL) was stable to 18 h in NS. Higher-concentration treprostinil (1.0 mg/mL) with dopamine (40.0 mg/mL) was not physically or chemically stable. Treprostinil (0.4, 1.0 mg/mL) and epinephrine (8.0, 90.0 µg/mL) was not physically or chemically stable. Treprostinil (0.4, 1.0 mg/mL) and epinephrine (8.0, 90.0 µg/mL) stability was inconclusive due to epinephrine standard degradation. Lower-concentration treprostinil (0.4 mg/mL) was stable to 24 h in NS with: dexmedetomidine (4.0 µg/mL); dobutamine (1.0 mg/mL); fentanyl (10.0 µg/mL); furosemide (1.5 mg/mL); midazolam (0.1 mg/mL); milrinone (0.2 mg/mL); morphine (5.0 mg/mL); norepinephrine (16.0 µg/mL); and vasopressin (2.0 units/mL). Higher-concentration treprostinil (1.0 mg/mL) was stable to 24h in NS with: dexmedetomidine (4.0 µg/mL); dobutamine (8.0 mg/mL); fentanyl (50.0 µg/mL); furosemide (10.0 mg/mL); midazolam (5.0 mg/mL); milrinone (1.0 mg/mL); morphine (5.0 mg/mL); and norepinephrine (80.0 µg/mL). Treprostinil (0.4 mg/mL) with heparin (20.0 units/mL) was stable to 52 h in NS.

Conclusions: Treprostinil was physically and chemically stable at tested conditions when diluted in DS/D10W and when combined with 11 IV medications in NS.

When judgement trumps tissue: an unusual presentation of pulmonary veno-occlusive disease

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Background: Pulmonary veno-occlusive disease (PVOD) is a severe, progressive, rare lung pathology characterized by fibrous obliteration of pulmonary venules, leading to back pressure in the capillary and arteriolar network. Clinical presentation is similar to pulmonary arterial hypertension (PAH), with lung biopsy necessary to differentiate the diagnosis. Typical PAH therapy in PVOD causes pulmonary edema when precapillary vasodilation meets postcapillary resistance, as in the following case.

Case description: A 19-month-old child with a history of repaired tetralogy of Fallot presented with poor weight gain and decreased activity. Echocardiogram revealed a right to left shunt across a remaining atrial septal defect and ventricular septal defect. Cardiac catheterization showed elevated pulmonary vascular resistance with positive response to FiO2 1.0 and inhaled nitric oxide (iNO). Following catheterization, iNO was continued. Six hours later, severe pulmonary edema developed, leading to clinical suspicion for PVOD. Neither lung biopsy nor chest CT were consistent with PVOD. The child was transferred to our hospital after deterioration of respiratory status for transplant evaluation and pulmonary hypertension (PH) management. After transfer, the child was maintained on daytime high flow nasal cannula and nighttime non-invasive positive pressure with persistent tachypnea and hypoxemia. He was evaluated and approved for lung transplant listing due to strong suspicion of a missed PVOD tissue diagnosis. Unfortunately, the child had an acute episode of hypoxemia and hemodynamic instability resulting in cardiac arrest and death. Autopsy revealed classic findings of PVOD that were not seen on initial imaging and lung biopsy.

Discussion: PVOD is a rare and difficult to diagnose presentation of PH that may not have typical PVOD findings during diagnostic evaluation despite convincing clinical findings. Treatment options are limited, with lung transplant as one of the only effective endpoints. Early referral to a Pulmonary Hypertension Center with a Lung Transplant Center is recommended for suspected PVOD.

Impaired biventricular response to exercise in adolescents born preterm

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Background: Recent evidence suggests that young adults born preterm have higher incidence of hypertension, cardiac dysfunction, and exercise intolerance. We investigated whether adolescent children have impaired exercise tolerance, and whether it is in part due to cardiovascular dysfunction during exercise.

Materials and Methods: Children born preterm in 2003 and 2004, weighing < 1500 g with an average gestational age of 28 weeks, and healthy age-matched term controls were studied. Participants underwent cardiac MRI at both rest and 70% Pmax on a supine stepper (Cardio Step Module, Ergospect Medical Technology, Innsbruck, Austria). Resting cardiac structure and function measurements were acquired by cardiac MRI by a 3-T GE scanner. Exercise SV was determined using 2D flow through...
the main pulmonary artery and aorta. Statistics were performed using Mann–Whitney tests and two-way ANOVA, and significance was determined as \( P < 0.05 \). Results are reported as mean ± SD.

**Results:** At rest, preterms had lower LV end-diastolic volume index (LVEDVi) (72.9 ± 9.5 vs. 84.2 ± 7.2 mL/m \(^2\), \( P = 0.02 \)), lower LV end-systolic volume index (LVESvi) (45.3 ± 6.9 vs. 31.0 ± 5.7, \( P = 0.03 \)), lower RVEDVi (72.8 ± 13.8 vs. 82.3 ± 11.2, \( P = 0.03 \)), and lower RVESVi (29.0 ± 6.6 vs. 34.5 ± 6.5, \( P = 0.01 \)). Aortic pulse wave velocity (PWV) was significantly higher in preterms than controls (5.9 ± 3.0 vs. 3.9 ± 1.2 cm/s, \( P = 0.02 \)). Right ventricular stroke volume index (RV-SVi) at rest was not different between groups; however, RV-SVi augmented significantly during exercise in controls (rest: 52.5 ± 8.3, ex: 97.8 ± 25.1 mL/m \(^2\), \( P < 0.01 \)), but not in preterms (rest: 52.5 ± 10.8, ex: 58.9 ± 15.1 mL/m \(^2\), \( P = 0.14 \)).

**Conclusion:** Preterm birth is associated with impaired exercise tolerance, high aortic PWV, and abnormal resting cardiac function. Our study demonstrated that exercise intolerance in adolescents born preterm is likely due to a blunted SV reserve during exercise, with potentially clinically significant impairment in RV function.

**Pharmacokinetics of oral treprostinil in children with pulmonary arterial hypertension**

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**Background:** Orenitram® (treprostinil) is an FDA-approved, oral prostacyclin analogue for treatment of pulmonary arterial hypertension (PAH) in adults. In this open-label study, we examined the pharmacokinetics (PK) of oral treprostinil in children (NCT02276872).

**Materials and Methods:** Oral treprostinil was given to individuals in one of three groups; parenteral treprostinil transition (cohort 1); inhaled treprostinil transition (cohort 2); and de novo (cohort 3). Oral treprostinil was dosed three times daily (TID); one individual in cohort 3 transitioned to four times daily (QID) dosing. PK samples were obtained before and at 2 h, 4 h, 6 h, and 8 h after a dose of oral treprostinil. For cohort 1, baseline parenteral PK samples were obtained. PK parameters were calculated using noncompartmental analysis.

**Results:** Thirty-two children (\( n = 10 \) in cohorts 1 and 2, \( n = 12 \) in cohort 3) were enrolled; median age 12.0 years (range 7–17 years) and weight 42.2 kg (range 19.3–78 kg). Median oral treprostinil dose was 3.81 mg, 5.88, 3.50, and 4.00 mg for cohorts 1, 2, and 3, respectively. Following oral administration, the treprostinil concentration vs. time profile demonstrated a peak concentration at a median of 3.87 h (range 0–6 h). In cohort 1, peak concentrations after oral treprostinil were higher (7.39 ng/mL and trough concentrations were lower (1.17 ng/mL) compared with parenteral (C\(_{\text{max}}\) 5.44, C\(_{\text{min}}\) 3.75 ng/mL). Parenteral C\(_{\text{avg}}\) was 4.51 ng/mL, while C\(_{\text{avg}}\) after oral treprostinil was 4.09, 2.34, and 3.09 ng/mL, respectively. Dose- and weight-normalized parameters for treprostinil exposure (C\(_{\text{max}}\) and AUC) were similar among cohorts but significant fluctuations were noted without clear relationship to age or body weight.

**Conclusions:** In this study, C\(_{\text{avg}}\) after oral dosing of oral treprostinil was lower when compared with parenteral treprostinil, likely due to non-comparable dosing. Time to C\(_{\text{max}}\) and individual PK curves were found to be highly variable; QID dosing was given in one patient. Additional study is required to determine the optimal dose and dosing strategy in pediatric patients.

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**Loss of reversibility in flow-induced pulmonary arterial hypertension is associated with a senescent vascular phenotype**

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**Background:** Patients with a left-to-right shunt due to congenital heart disease (CHD) are at risk of developing progressive pulmonary arterial hypertension (PAH). While timely hemodynamic unloading (HU) by shunt closure usually reverses the arteriopathy, the timepoint when or reason why PAH becomes irreversible has been difficult to ascertain.

**Materials and Methods:** PAH was created in syngeneic rats by monocrotalin injection at t0 days and a surgical aorto-caval shunt (t7). For HU at different PAH stages, the left donor lung with PAH was transplanted into healthy recipients at t14, t21, or t28 of the model. Recipients were sacrificed 21 days after transplantation.

**Results:** Monocrotalin + shunt induced medial neomuscularization from t14, and neointimal lesions from t21, causing progressive arteriolar occlusion and PAH. HU normalized the vascular morphology in all t14 rats and in 7/10 t21 rats, whereas no reversal or progressive occlusion occurred in 3/10 t21 and all t28 rats. RNA-sequencing performed on donor lung tissue harvested at HU revealed that activated pro-proliferative/ regenerative, pro-apoptotic, and DNA-repair pathways were associated with reversal after HU. This was confirmed immunohistochemically by increased vascular-specific Ki67, Caspase3, and Rad51 protein expression. In contrast, disease
IGFBP2 is associated with pediatric pulmonary hypertension and disease severity

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Background: Pulmonary arterial hypertension (WHO Group I PAH) in children is a progressive, fatal disease characterized by sustained elevation of pulmonary arterial pressures (PAPs) and with the mechanism largely unknown.

Objective: Using an unbiased mass spectrometry plasma proteomics discovery approach, we identified insulin-like growth factor binding protein 2 (IGFBP2) as a possible biomarker of PAH and determined the relationship of IGF1, IGF2, and IGFBP2 in pediatric PAH.

Materials and Methods: Plasma samples (n = 125, 3–21 years, 49% IPAH, 59% female) were obtained from the NHLBI PAH Biobank as well as an independent cohort of controls (n = 63, age 4 days–21 years, 43% female) with no cardiopulmonary disease. We measured plasma concentrations of total IGF1, IGF2, and IGFBP2 using commercial ELISAs. Concentrations of IGF1, IGF2, and IGFBP2 were compared with controls (Wilcoxon rank-sum test). A subset of the PAH cohort had invasive cardiac hemodynamics available (n = 26) with mean PAP (mPAP), mean right atrial pressure (mRAP), and pulmonary vascular resistance (PVR, m2 with test occlusion of the PDA on oxygen and iNO). The hemodynamics immediately after the procedure and the time taken for the return to pre-procedure RSS, and the time taken for the RSS to get a score of <2 were measured. Factors contributing to prolonged elevation of RSS ≥2 were identified using a Cox Proportional Hazard Model.

Results: Median plasma IGFBP2 concentrations were increased in the PAH cohort (279.1 ng/mL, IQR 175.2–400.2 ng/mL) compared with controls (80.5 ng/mL, P < 0.001). Total IGF1 (118 ng/mL, IQR 71.6–194.8 ng/mL) was increased in the PAH cohort compared with controls (72.44 ng/mL, IQR 41.7–116.7 ng/mL, P = 0.001). Cardiac hemodynamics were used as measures of clinical severity. The PAH Biobank cohort had a mPAP of 52 mmHg and PVR of 24.7 Woods units × m2. IGFBP2 concentrations significantly correlated with mPAP (r = 0.55, P = 0.036) and approached statistical significance with mRAPs (r = 0.37, P = 0.0716), but had no relationship with PVR. By contrast, NT-ProBNP had no relationship with mPAP or right mRAP (r = 0.26, P > 0.1). IGFBP2 also demonstrated significant diagnostic sensitivity and specificity for PAH with an area under the ROC curve of 0.91 (P < 0.001, 95% CI 0.86–0.94).

Conclusion: IGFBP2 and IGF1 concentrations are different in PAH patients compared with controls and IGFBP2 correlated with hemodynamic measures of disease severity and was a sensitive and specific diagnostic for PAH. Notably, IGFBP2 outperformed NT-ProBNP, the current standard of care PAH biomarker, in hemodynamic measures of disease severity. This suggests that dysregulation of the IGF axis could play a role in the pathobiology of pediatric pulmonary hypertension and provide added value to current clinical measures to diagnose and monitor PAH severity.

Hemodynamic effect of timing of transcatheter device closure of the preterm ductus arteriosus

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Background: Patent ductus arteriosus (PDA) is common in extremely low birth weight (ELBW) infants (BW < 1 kg). Transcatheter PDA closure (TCPC) allows for hemodynamic assessment in ELBW infants. The objective of this study was to compare respiratory outcomes of ELBW infants that underwent early (≤ 4 weeks of age) vs. delayed (> 8 weeks of age) PDA closure.

Materials and Methods: A retrospective review was performed comparing respiratory outcomes of infants born at a gestational age (GA) of ≤ 27 weeks, weighing ≤ 1 kg at birth, and PDA size ≥ 2 mm referred for TCPC. Only children that survived at least one year after TCPC were included in the study. Those who did not have hemodynamic assessments were excluded. Baseline respiratory severity scores (RSS) were calculated for all. Hemodynamic assessment included a baseline Qp:Qs ratio, pulmonary artery systolic pressure (sPAP) as a percentage of the systolic blood pressure (SBP), and indexed pulmonary vascular resistance (PVRi). If the baseline PVRi was ≥ 4 WU*m2, then pulmonary vasodilator therapy using inhaled nitric oxide (iNO) and 100% oxygen is performed. This was followed by re-measurement of hemodynamics with test occlusion of the PDA. The Qp:Qs and PVRi were calculated for all three conditions. The PDA was occluded only if the PVRi was ≤ 4 WU*m2 with test occlusion of the PDA on oxygen and iNO. The RSS immediately after the procedure and the time taken for the return to pre-procedure RSS, and the time taken for the RSS to get a score of <2 were measured. Factors contributing to prolonged elevation of RSS ≥2 were identified using a Cox Proportional Hazard Model.

Results: The study included 27 ELBW infants that underwent TCPC ≤ 4 weeks (Group 1), 23 infants that underwent TCPC
Background: Congenital diaphragmatic hernia (CDH) is a common and severe congenital malformation. The risk of mortality in CDH patients is due to abnormal development of the lungs and pulmonary vasculature causing pulmonary hypoplasia and pulmonary hypertension (PH). The severity of these defects is variable and their developmental origins are unclear. Our hypothesis is that a core group of genes is required for diaphragm development and development of the lungs and pulmonary vasculature. Mutation of these genes may be responsible for pulmonary hypoplasia and PH in CDH patients. SIN3A gene mutations have recently been identified in patients with CDH; however, its role in diaphragm, lung, or pulmonary vascular development is not clear. Our hypothesis was that SIN3A is required for diaphragm, lung, and pulmonary vascular development.

Materials and Methods: Using a tissue-specific, conditional-knockout approach in mice, we inactivated the expression of Sin3a in either the developing diaphragm or lung mesenchyme. We used histology, gene expression analysis, and physiology to analyze the phenotype.

Results: Deletion of Sin3a in the developing diaphragm muscle results in a mouse model of CDH due to decreased cellular proliferation. Furthermore, deletion of Sin3a in the developing lung results in pulmonary hypoplasia, failure of alveologensis, and PH due to abnormal mesenchymal and lung vascular development.

Conclusion: Mutations of the SIN3A gene have been identified in human CDH. Tissue-specific deletion of Sin3a results in a novel mouse model of CDH and Sin3a is required in the developing diaphragm muscle. Furthermore, lung-specific deletion of Sin3a results in pulmonary hypoplasia, failure of alveologensis, and PH. These data support the model that genetic defects in CDH patients can cause abnormal development of the lungs independent of the diaphragm defect. We plan to identify the downstream molecular mechanisms responsible for PH in Sin3a mutant mice, and derive a therapeutic approach that reverses these molecular defects.

A case of pulmonary arterial hypertension secondary to scurvy in a developmentally typical child

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Background: Scurvy, the clinical syndrome of vitamin C deficiency, has been well recognized to include musculoskeletal pain, fatigue, petechial hemorrhage, and bleeding gums since the 18th century. Three prior case reports, all in patients with intestinal malabsorption or severe developmental delays, have described reversible pulmonary arterial hypertension (PAH) associated with scurvy. Animal studies suggest tolerance to endogenous nitric oxide signaling as a potential mechanism. There is no previous report of scurvy-induced PAH in a developmentally typical and thriving child.

Case description: WM is a 17-year-old boy with a history of HLA B27+ spondyloarthritis who presented with two weeks of worsening leg pain, bruising, chest pain, and shortness of breath. Review of systems revealed exercise intolerance, gum bleeding, and a restrictive, junk food diet devoid of fruits and vegetables. There was no history of trauma. Physical exam was notable for loud P2, symmetric pedal edema, bilateral lower extremity tender ecchymosis, petechiae, and corkscrew hairs. Echocardiogram showed a structurally normal heart with a peak tricuspid regurgitation (TR) velocity of 4.2 m/s. Lower extremity Doppler ultrasound, chest CT, and bilateral leg MRI were normal. Hypercoagulability evaluation and inflammatory markers were unremarkable. Due to the characteristic cutaneous findings, vitamin C level was sent and returned undetectable, consistent with scurvy. One month after initiating vitamin C supplementation, the peak velocity of TR had decreased to 3.1 m/s and the patient’s symptoms had resolved.

Discussion: Given the guarded prognosis associated with idiopathic PAH, a thorough search for an underlying cause is essential in all new PAH cases. We present the first case of scurvy-induced PAH in a developmentally typical, thriving child with no signs or symptoms of gastrointestinal disease. PAH severity and associated clinical symptoms improved after vitamin C supplementation.
repletion. Thorough dietary history and cutaneous exam were crucial to the diagnosis of this unusual etiology.

**Right ventricular strain evaluation by a novel 16-segment method in healthy children**

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**Background:** Right ventricular (RV) longitudinal myocardial strain is not being routinely used for clinical decision-making in children. Studies to date have reported six-segment or three-segment strain which leaves a larger part of the RV unattended. The RV, being a 3D non-globular structure, can be better represented with 16 segments like the standard left ventricular strain method. Such a method has been recently published for adults. We aimed to obtain normal values of RV strain by 16-segment methods in healthy children.

**Materials and Methods:** Healthy children aged 5–18 years were selected from the cardiology clinic. RV images were acquired prospectively as described by Forsha et al. (2014). Children with an abnormal echocardiogram, a history of congenital heart disease, or cardiomyopathy were excluded from the study. RV strain analysis was performed using TomTec 5.5.1 (Chicago, IL, USA). Descriptive statistics was reported as mean ± SD. Difference between the means were calculated using t-test with significance level of P < 0.05.

**Results:** There were 32 patients that met criteria for evaluation. The mean age of patients was 10 ± 4.52 years. The male:female ratio was 1:1. The mean global RV strain was −26.1 ± 4.4%. There was a base (−33.9 ± 12.8%) to apex (−16.9 ± 9.8%) strain gradient as noted by previous studies. RV free wall strain was −30.1 ± 9.2% significantly different compared to the septal strain of −24.3 ± 9.2% (P = 0.04).

**Conclusion:** This is the first study demonstrating comprehensive functional evaluation of RV by the 16-segment strain model in healthy children. Mean RV strain in healthy children based on this model is −26.1 ± 4.4%. Regional RV wall strain differences can be negated by using the comprehensive 16-segment method. User-friendly image acquisition protocol may allow use of this model to characterize abnormal RV function in diseased RV.

**MicroRNA-21 predicts functional status in children with pulmonary hypertension associated with congenital heart disease**

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**Background:** Pulmonary hypertension (PH) is a life-threatening condition with a five-year mortality of 65–75% in children. The most important predictor of mortality is the ability of the right ventricle (RV) to adapt to elevated pulmonary pressures. There is a critical need for RV-specific biomarkers to assess the mechanism of RV adaptation in PH. We have shown that plasma microRNA-21 (miR-21), a pro-fibrotic marker, increases with increasing tissue fibrosis in children with tetralogy of Fallot. We hypothesize that plasma miR-21 expression will increase with disease severity in children with PH with congenital heart disease (CHD).

**Materials/Methods:** A cross-sectional study of children with PH with collection of blood samples from June 2014 to October 2017 were studied. Plasma miR-21 expression was assessed using qRT-PCR and correlated with demographic and clinical data at the time of collection.

**Results:** Matched patient data and blood samples were available on 35 patients with PH. For this study, we evaluated children with PH with associated CHD (n = 21) including atrioventricular septal defects, left-to-right shunts, anomalous pulmonary venous return, and conoventricular defects. miR-21 expression did not correlate with duration of PH. miR-21 expression increased with worsening Panam2 functional status: 1 vs. 1.86 vs. 2.1-fold (P < 0.05). miR-21 expression decreased by 1.7-fold in patients on systemic pulmonary vasodilatory therapy (n = 7) vs. patients on oral therapy (n = 8). miR-21 expression correlated positively with NT-proBNP (r = 0.64) and pulmonary capillary wedge pressure (r = 0.55) and negatively with cardiac index (r = 0.89) (P < 0.05).

**Conclusions:** Plasma miR-21 expression increases with worsening functional status and may suggest increasing RV myocardial fibrosis and cell death. Lower miR-21 levels in patients on systemic vasodilatory therapy may indicate a subgroup of patients within a functional class who have undergone favorable remodeling. Plasma miR-21 expression may add prognostic value to current biomarkers in children with PH and associated CHD.

**Left ventricular vorticity by 4D flow MRI as a marker of left ventricular diastolic dysfunction in pediatric pulmonary arterial hypertension**

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**Background:** Studies have demonstrated impaired left ventricular (LV) diastolic function by echocardiography in pulmonary arterial hypertension (PAH). 4D flow MRI allows for non-invasive evaluation of the flow domain providing novel data in combination with conventional measurements. In adults with PAH, baseline peak diastolic vorticity is decreased and correlates with ventricular interdependency and diastolic dysfunction; however, it is unclear how iNO affects either entity. We hypothesize that iNO challenge will alter an already abnormal LV diastolic function as reflected by vorticity in pediatric PAH patients.

**Materials and Methods:** Pediatric PAH patients underwent right heart cardiac catheterization and 4D flow MRI assessment.
on a 3-T Philips scanner (Philips Medical Systems) within 60 days of each other. Acute vasoreactivity testing (AVT) was performed in the catheterization suite and MRI scanner with 4D imaging. 4D flow MRI was obtained using a retrospective, cardiac-gated gradient echo sequence, reconstructed over one cardiac cycle. Velocity and vorticity data were processed in ParaView (Kitware, Clifton, NY, USA). The LV was segmented at peak diastole to include the volume from the mitral valve annulus to the apex. Vorticity field was defined as the summation of vorticity vectors during early diastolic phase.

**Results:** Six patients (mean age 13.6 ± 3.8 years) were included. One patient had positive AVT response. At baseline and AVT, the velocity vectors lack normal circulatory formation from the mitral valve anterior leaflet. Mean LV diastolic vorticity field decreased from 28,378 ± 7581 s⁻¹ to 20,561 ± 6079 s⁻¹. Compared to baseline, the diastolic vorticity field appears decreased and approaches zero at the endocardial borders under AVT conditions.

**Conclusion:** LV peak diastolic vorticity is altered in pediatric PAH patients under iNO challenge. This change may reflect a further decrease in LV diastolic function or acute changes in ventricular interdependence that is sensitive to therapeutic interventions.

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**Transcatheter ventricular septal defect creation as an innovative, non-surgical therapy for severe pulmonary hypertension with right ventricular failure: a case Series**

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**Background:** Despite improved pharmacotherapy in recent years, pediatric pulmonary hypertension (PH) carries a high risk of morbidity, such as right heart failure, and mortality. Currently, there are few palliative options utilized to decompress the right ventricle (RV) in these patients.

**Case descriptions:** Case 1 is a 14-year-old girl with suprasystemic idiopathic PH and Turner syndrome on tadalafil, ambrisentan, and IV treprostinil with worsening severe right heart failure. A transcatheter ventricular septal defect (VSD) was created based on hemodynamics suggesting an atrial septal defect (ASD) would shunt preferentially left to right. The patient had improvement in RV function and resolution of severe heart failure. Case 2 is a five-year-old boy with suprasystemic PH secondary to lung hypoplasia associated with congenital diaphragmatic hernia on tadalafil, ambrisentan, and subcutaneous treprostinil with worsening right heart failure despite an ASD. Recanalization of the ductus arteriosus was attempted but unsuccessful; therefore, a transcatheter VSD was created. The patient had improvement in RV function before discharge. Case 3 is an 11-year-old boy with pulmonary veno-occlusive disease and severe PH who required venoarterial (VA) extracorporeal membrane oxygenation (ECMO) due to hemodynamic instability. Patient underwent creation of an ASD and VSD which allowed conversion to venovenous (VV) ECMO, listing for transplant, and ultimately bilateral lung transplant with closure of his septal defects.

**Conclusion:** Transcatheter VSD creation presents a viable, innovative technique to decompressing the RV and has created excellent results without intraoperative complications in our series of three patients.

**Does accelerometry provide more accurate real-time information to evaluate and follow-up patients with pulmonary arterial hypertension?**

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**Background:** Pulmonary arterial hypertension (PAH) remains a disease with high morbidity and mortality. Functional capacity testing including 6-min walk distance (6MWD) and cardiopulmonary exercise testing (CPET), which are traditionally used for baseline evaluation and monitoring of therapy and as clinical endpoints, do not provide real-time data and provide a snapshot of effort tolerance at the time of the visit. The purpose of this single-center prospective study is to evaluate the use of a Fitbit Charge HR as a novel tool to obtain real-time evaluation of effort in PAH patients and to determine if wearing a Fitbit alone can motivate patients to increase their daily activity levels and improve quality of life (QoL).

**Materials and Methods:** Individuals aged ≥ 13 years with WHO functional class (FC) I–III who underwent a 6MWD and CPET were enrolled and given a Fitbit with instructions on uploading data periodically to a cloud-based database. Data obtained included demographics, PAH classification, WHO FC, 6MWD, and CPET. Fitbit data included levels of activity, steps per day, heart rate, and calories expended. Participants were given a QoL questionnaire (SF-36) at baseline and follow-up visits 12–16 weeks later. Patients were not prescribed an exercise regimen at baseline in order to determine if the use of the physical activity tracker alone motivated the individuals to increase activity levels. At follow-up, patients were randomized into an intervention and non-intervention group, to evaluate if introducing an individualized exercise regimen would impact outcomes after one year.

**Results:** Twenty-seven individuals (15 girls, 12 boys; age range 13–59 years) were enrolled. At baseline, 22% (6) patients were in WHO FC I, 48% (13) FC II, and 30% (8) were in FC III. Average 6MWD in FC I was 524 m, FC II 495 m, and FC III 388 m. Fitbit data from the first two weeks of tracking were compared with the 6MWD and CPET data at the baseline visit. Average steps taken per day was a significant predictor of
6MWD (P < 0.001) with an \( r^2 \) value of 0.883. Significant predictors were found between 6MWD (\( r^2 = 0.96 \) for 6MWD) and average steps, distance walked, calories burned, and activity through multivariable analysis. The QoL questionnaire revealed improved vitality scores on follow-up in 77% (\( P = 0.008 \)), improved social functioning in 70%, improved pain scores in 92%, and improved emotional wellbeing and general health in 70% and 62%, respectively.

**Conclusion:** The Fitbit provides real-time data, which correlates well with baseline 6MWD and CPET and provides longitudinal data on activity levels that could be used to monitor therapy and as potential endpoints for future clinical trials. Use of a Fitbit incentivizes patients to increase their activity levels and thereby improves their QoL as certain symptoms of PH such as fatigue significantly decreased over 12–16 weeks.

**Selexipag in three pediatric patients**

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**Background:** We describe the experience of selexipag in three pediatric PH patients. Adult dosing begins at 200 mcg and titrates up by 200-mcg increments. Tablets are film-coated to protect them from light. However, there are no dosing guidelines or published reports of selexipag use in children.

**Case descriptions:** Patient 1 is a seven-year-old girl with Trisomy 21, pulmonary hypertension associated with repaired congenital heart disease and chronic lung disease on tadalafil and bosentan. Selexipag was initiated at 50 mcg twice daily and titrated by 50–100 mcg to 800 mcg twice daily. Titration was achieved by cutting 200 mcg tablets and administering them orally. The unused portion was stored in a dark medication bottle. Patient 2 is a two-year-old girl with single ventricle physiology on sildenafil. Selexipag was initiated at 50 mcg twice daily and titrated by 50–100 mcg to 400 mcg twice daily. Titration was achieved by dissolving 200 mcg tablets in 10 mL of tap water, discarding the appropriate volume to achieve correct dose, and administering the final dose via gastric tube. Patient 3 is a six-year-old girl with Eisenmenger syndrome, on tadalafil. Selexipag was initiated at 100 mcg twice daily and titrated by 100 mcg weekly to 300 mcg twice daily. Titration was achieved by cutting 200 mcg tablets, dissolving the cut tab in water, and administering orally. The unused portion was stored in a dark medication bottle.

**Results:** At five-month follow-up, patient 1 was unchanged. At one-month follow-up, patients 2 and 3 had improvement in oxygen saturations and patient 3 reported improved endurance. Patient 1 had side effects of diarrhea, emesis, and body aches. Patient 2 had no side effects. Patient 3 had diarrhea.

**Conclusion:** Children with PH can be titrated on selexipag by cutting and/or dissolving selexipag tablets and administered orally or by gastric tube.