1.1 Pulmonary arterial stroke volume: A new and strong prognostic factor in pediatric pulmonary arterial hypertension

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In the current era of evolving treatment options, there is a need for reliable prognostic parameters in pediatric pulmonary arterial hypertension (PAH). The purpose of this study was to determine the prognostic value of pulmonary stroke volume (PSV) and pulmonary arterial compliance (stroke volume / pulse pressure; PAC) in pediatric PAH. Cardiac catheterization data of 50 consecutive children with idiopathic/hereditary PAH (iPAH/HPAH; n=30) or PAH associated with congenital heart disease (PAH-CHD; n=20) were retrospectively reviewed. PSVI and PACI (both indexed for body surface area) were determined at baseline and during acute vasodilator response tests (AVR). Survival analyses were performed using Kaplan Meier curves and (multivariate) Cox Regression analyses, using death or lung transplantation as endpoints. PSVI (38.4±25.4 ml/m²) and PACI (0.97±0.83 ml/mmHg/m²) were both age-independent and did not differ between iPAH/HPAH and PAH-CHD. During AVR, PSVI increased to 45.6±25.4 ml/m² (P=0.01) and PACI to 1.80±2.87 ml/mmHg/m² (P=0.01). In univariate analysis, higher baseline PSVI and PACI were associated with improved outcome. In multivariate analysis, corrected for diagnosis, systemic to pulmonary shunt, gender, age, drug-treatment, mean right atrial pressure, cardiac index and pulmonary vascular resistance index, baseline PSVI independently predicted prognosis (HR 0.25 [95% CI 0.07-0.88] per SD P=0.03); in contrast, PACI did not predict prognosis. PSVI and PACI during AVR did not have additional prognostic value. Baseline PSVI is a strong independent predictor for prognosis in pediatric PAH and may be used to identify higher-risk patients and guide therapy.

1.2 High morbidity and mortality in premature infants with pulmonary arterial hypertension secondary to bronchopulmonary dysplasia

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Pulmonary arterial hypertension (PAH) is the most significant cardiovascular complication of bronchopulmonary dysplasia (BPD), a chronic lung disease affecting 15,000 premature infants in the US yearly. Despite reported high mortality in these patients, there is paucity of data on its onset and clinical outcomes. We reviewed the characteristics, onset of PAH, medical therapy, morbidity and mortality in 24 BPD patients with PAH. PAH was established by echocardiography and/or cardiac catheterization. Their mean gestational age was 25.7±1.7 weeks and mean birth weight was 679±259 grams. Among the 24 babies, 54% were females and 46% were born small for gestational age. PAH was initially diagnosed at 106±56 days of life, mainly by echocardiography. Since they had a previous normal echocardiogram at 47±44 days, we predict that PAH can be manifested in BPD patients as early as 2 months of life. Eighty-three percent of patients had Nissen fundoplication and G tube placement, 50% had patent ductus arteriosus ligature and 75% had tracheostomy tubes. Five out of 24 infants died (21%) with 2 occurring in hospital. Twenty-two survivors were discharged on either a home ventilator or nasal cannula at 6.9±2.7 months. All except 2 were on pulmonary vasodilators, most frequently sildenafil (91%). During the first year after discharge, there was an average of 3 hospital readmissions per patient, with 30/62 (48%) readmissions due to pneumonia and BPD exacerbation. On follow-up (28±14 months), 50% of children continued to have weights below the 10th percentile. Clinically significant PAH may begin at 2 months of age in preterm babies with BPD. These infants have poor growth, significant co-morbidities, frequent readmissions after discharge and a high mortality rate. There is a need to improve surveillance and management of these high-risk patients.

1.3 Non-invasive assessment of right heart and pulmonary vascular coupling in children with pulmonary hypertensive vascular disease: A simultaneous echocardiographic and catheterization study

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Cardiac catheterization is the gold standard for assessment of hemodynamics in children with pulmonary hypertensive vascular disease (PHVD). There is a need for accurate, non-invasive correlates of these hemodynamics. The aim of this study was to identify correlations between echocardiographic and catheter parameters in children undergoing cardiac catheterization to investigate PHVD. Echocardiograms were performed on patients with PHVD undergoing cardiac catheterization, after induction of anesthesia. Echocardiographic parameters assessed included tricuspid valve (TV) annular tissue Doppler velocities (TDI), TV inflow Doppler; right atrial (RA) and right ventricular (RV) dimensions and function. Cardiac catheterization data included RA and RV pressures, pulmonary arterial pressure (PAP), pulmonary blood flow, pulmonary vascular resistance index [PVRI], pulmonary capacitance index (PCI) and cardiac index (CI). We studied 14 consecutive patients (8 male; median age 6 years, range 1 - 15) with mean PAP 42±22 mmHg and PVRI 13±6 WU/ml. TV peak regurgitant velocity correlated with systolic PAP (r=0.79, P<0.01) suggesting patients were studied under the same hemodynamic conditions. RA mean pressure correlated with TV E/e' prime ratio (r=0.67, P=0.02). There was no correlation between echocardiographic parameters of RV function (TAPSE, MPI, TV S' prime) and catheter parameters. PVRI correlated with TV TDI a prime (r=-0.56, P=0.03). CI correlated with TV inflow E velocity time integral (VTI) (r=0.82, P<0.01). PCI correlated negatively with RA fractional area change (FAC) (r=-0.62, P=0.03) and TV inflow E (r=-0.72, P=0.01). In conclusion, we have demonstrated a correlation between invasive hemodynamic data and echocardiographic
parameters in children with PHVHD. TV inflow Doppler and annular TDI velocities correlate to PVRI, PCl, C1 and RA pressure. These measures may be useful non-invasive markers of PHVHD progression or treatment response. This data also suggests increased reliance on atrial function for RV filling in patients with PVHD. This requires further investigation in our patient population.

1.4 Right ventricular adaptation in a mouse model of sickle cell disease: Does N-terminal deletion of cardiac troponin play a role?

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Sickle cell disease (SCD) is characterized by disturbances in pulmonary vascular blood flow, predisposing patients to pulmonary hypertension (PH), subsequent elevation of right ventricular pressure and complete right ventricular failure in severe cases. Although the response of the right ventricle to pressure overload is a critical determinant of outcome, little is known about the molecular determinants of right ventricular adaptation to elevated pressure. Jin and colleagues recently described a novel post-translational restricted N-terminal proteolysis of cardiac troponin T (cTnT-ND) in response to left ventricular pressure overload. This novel adaptation modifies cardiac muscle contractility in response to left ventricular pressure overload to maintain cardiac output. We hypothesized that the right ventricle in a sickle cell mouse model undergoes a similar molecular adaptation in response to pressure overload. N-terminally deleted cTnT was measured in hearts from wild-type (AA), heterozygote (AS) and homozygous (SS) sickle mice (UAB). Hearts were extracted, right and left ventricle dissected, homogenized, prepared in sample buffer and resolved via SDS gel electrophoresis. cTnT fragments were detected via Western blot. The right ventricle to total heart weight ratio was significantly larger in SS mice (0.1367±0.0376) versus AS and AA mice [0.0995±0.0148]. Quantitation analysis showed a higher ratio of modified cTnT-ND to full length cTnT in right ventricular tissue from homozygous SS mice (0.296; n=10) compared to heterozygote AS (0.122; n = 9) and wild type mice (0.157; n = 6). The increased post-translationally modified cTnT-ND observed in SS mice right ventricular tissue is the first description of this adaptive response selectively in the right ventricle and the first description of this adaptive response in a chronic disease model. The increased RV weight in SS vs AA/AS mice is also consistent with previous data confirming that SCD mice have elevated pulmonary vascular pressures. As observed in previous models of left ventricular pressure overload, we believe the increased cTnT-ND levels reflect a functional adaptation to elevated right ventricular pressure. This is the first demonstration of cTnT post-translational modification in the context of an intact chronic disease model, and suggests a novel role for cTnT-ND in right ventricular functional adaptation in the context of sickle cell disease.

1.5 Acute hemodynamic effects of inhaled treprostinil and nitric oxide in children with pulmonary arterial hypertension

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The safety and acute pharmacodynamic effects of inhaled treprostinil (iTRE) in children with pulmonary arterial hypertension (PAH) is unknown. This study describes the feasibility and safety of delivering iTRE to sedated or anesthetized children during cardiac catheterization. Twelve children, median age 10.9 years (range 4.6-18.8) with known and treated PAH underwent catheterization as part of routine follow-up while sedated or anesthetized. Diagnoses included IPAH (n=5), PAH-CHD (n=5) and other APAH (n=2). Standard reactivity testing was first performed with oxygen plus nitric oxide (iNO-O2 40 ppm). Following return of the hemodynamic status to baseline, 3-6 breaths of iTRE was delivered, followed by 3-6 additional breaths for a maximum of 9 breaths if tolerated. iTRE was administered using the OPTINEB®-ir Model ON-100® ultrasonic nebulizer via either a non-self inflating bag or manual mode of the anesthesia system in synchrony with the Optineb’s inhalation indicator. iTRE was successfully delivered to children during cardiac catheterization. The median tolerated dose was 9 breaths (1.6 mcg/kg). Acute hemodynamic response to iTRE and iNO-O2 were similar. Baseline mPAP of 38±9 mmHg decreased to 32±8 mmHg with both agents. Pulmonary resistance index decreased from 7.3±2.9 units x m2 at baseline to 5.7±2.6 and 5.6±2.2 units x m2 with iNO-O2 and iTRE respectively, without a decrease in SVRI overall. A mild fall in systemic blood pressure was noted in 2 children when dosed beyond 6 breaths and 1 child experienced cough. In a small cohort of pediatric PAH patients, iTRE was successfully delivered during cardiac catheterization. The acute hemodynamic response to iTRE was similar to iNO-O2; however, higher dose iTRE may be associated with a mild fall in systemic blood pressure. Further investigation is warranted regarding use of iTRE the critical care setting and chronic use in children.

1.6 Pulmonary interstitial glycogenosis: An unrecognized etiology of PPHN in congenital heart disease?

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Pulmonary interstitial glycogenosis (PIG) arises from a developmental disorder of the pulmonary mesenchyme, and presents clinically with reversible neonatal respiratory distress and/or persistent pulmonary hypertension of the newborn (PPHN). We report 2 cases of PIG in patients with congenital heart disease (CHD) and evidence of PPHN. Case #1: A term female infant with d-transposition of the great arteries, intact ventricular septum, an adequate patent foramen ovale and a patent ductus arteriosus, presented with persistent cyanosis and hemodynamic instability. PPHN was suspected, and inhaled nitric oxide was started with minimal response. Stress-dose hydrocortisone was started due to concern for cortisol deficiency. This coincided with clinical improvement. Normal ACTH and cortisol levels ruled out adrenal insufficiency, but an intraoperative lung biopsy confirmed the diagnosis of PIG. The post-operative course following an arterial switch procedure was uncomplicated. Case #2: A 37-day-old term male infant with a postnatal diagnosis of tetralogy, double-outlet right ventricle with pulmonary stenosis, underwent surgical repair. Intra-operatively, the distal pulmonary artery pressures and right ventricular pressure were noted to be near systemic. Surgical anatomic abnormalities were excluded, and a trial of inhaled NO had no response. The infant was extubated on postoperative day 1 and discharged home on oxygen. An intraoperative lung biopsy subsequently confirmed the diagnosis of PIG. Both cases demonstrated the hallmark PIG histologic finding of diffuse, uniform interstitial thickening due to the presence of immature interstitial cells containing abundant cytoplasmic glycogen. We report the second and third patients with PIG associated with CHD. Since histologic examination is required to establish the diagnosis, we speculate that PIG, while rare, may be under-recognized in neonates presenting with PPHN in the setting of CHD.
1.7 Measurement of oxygen consumption in children undergoing cardiac catheterization: A comparison between mass spectrometry and breath by breath methods

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Oxygen consumption (VO₂) is important in the calculation blood flow using the Fick equation. Measurement of VO₂ is difficult in intubated ventilated patients during the cardiac catheterization and reactivity testing. Assumed VO₂ introduces important errors in the calculation of pulmonary blood flow. VO₂ may be measured by mass spectroscopy (MS) using mixed expire argon dilution or by a breath-by-breath method (BBM) of gas exchange analysis. However, MS is expensive, demanding and unsuited to routine clinical use. BBM is simple to use but is unsuitable in mechanically ventilated children. We sought to compare VO₂ measurements by MS and BBM. Once a stable baseline was reached, we measured VO₂ continuously and simultaneously for 10 minutes by MS (Amis 2000, Innovision, Denmark) and BBM (Innoca, Innovision, Denmark) in consecutive anesthetized children, intubated with a cuffed endotracheal tube, mechanically ventilated and hemodynamically stable with normal body temperature undergoing cardiac catheterization. We studied 9 patients (7 female, median age 6 years range 0.4 -18, median weight 18 kg, 4 -73). Median VO₂, measured by MS was 5.4 ml/kg/min, interquartile range (IQR) 4.3-6.1 and by BBM was 4.9 ml/kg/min (IQR 4.7-5.5). The median difference between MS and BBM (0.4 ml/kg/min, 0.2-0.6) was not significant (P=0.074). The Spearman correlation between MS and BBM was high (R =0.86, P=0.003). Both MS and BBM may be used to measure VO₂ in anesthetized, intubated mechanically ventilated children undergoing cardiac catheterization. We found no difference in VO₂ measured by both methods in children >4 kg. We suggest that BBM method may be a useful alternative to MS to measure VO₂. BBM is ideal for clinical use with short set up times, easy calibration and inexpensive maintenance.

1.8 Pulmonary interstitial glycogenosis associated with pulmonary hypertension and hypertrophic cardiomyopathy

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We describe a neonate with pulmonary interstitial glycogenosis, pulmonary hypertension and hypertrophic cardiomyopathy. The fatal outcome in our patient contrasts with the reported favourable prognosis associated with isolated pulmonary interstitial glycogenosis. The association of pulmonary interstitial glycogenosis and hypertrophic cardiomyopathy to our knowledge, has not been reported previously. A male infant was born to a 36-year-old gravida 3, para 2, mennonite mother following an uncomplicated pregnancy and term spontaneous vaginal delivery with a birth weight of 3.1 kg. The initial diagnosis was transient tachypnea of the newborn. At 12 days of age an echocardiogram demonstrated severe pulmonary hypertension (RVSP 90 mmHg; systemic BP 57/28 mmHg). The patient was treated with NO at 20 ppm via nasal cannula and enteral sildenafil. At 16 days of age, he deteriorated with increasing respiratory distress, hypotension and clinical signs of a low cardiac output. He was intubated, mechanically ventilated and intravenous pressors administered. An open lung biopsy was performed at 27 days of age. The biopsy demonstrated features of pulmonary interstitial glycogenosis with well inflated lung tissue and diffusely expanded interstitium. The interstitial cells possessed vacuolated cytoplasm staining positively with periodic acid Schiff reagent for glycogen. The alveolar pneumocytes, pulmonary arteries and arterioles appeared normal. We did not administer steroids in case they would exacerbate the hypertrophic cardiomyopathy. The infant died at 71 days of age with sustained pulmonary hypertension and low cardiac output. The case is unusual because of the associated pulmonary hypertension and fatal, progressive hypertrophic cardiomyopathy. We have broadened the phenotype of pulmonary interstitial glycogenosis and demonstrated the diagnostic value of lung biopsy in a case of unexplained neonatal pulmonary hypertension.

1.9 Aggressive treatment of pulmonary hypertension in children with restrictive cardiomyopathy improves outcomes after cardiac transplant

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This study examines the effect of aggressive management of pulmonary hypertension in pediatric patients with restrictive cardiomyopathy, and assesses perioperative and one-year outcomes following heart transplant. Fifteen children with restrictive cardiomyopathy listed for transplant had cardiac catheterization for hemodynamic assessment and pulmonary reactivity. Patients were then placed on oral pulmonary vasodilators for mean pulmonary artery pressure greater than 25 mmHg or pulmonary vascular resistance (PVR) greater than 2.5 Wood Units (WU). Post-transplant, patients were followed with cardiac catheterization at weeks 1, 3, and 12; 6 months and one year. Seven treated patients were compared to three patients with normal pressures and 5 patients with untreated pulmonary hypertension. Five of the treated patients with pulmonary hypertension had documented changes in hemodynamics to the normal range prior to transplant; 2 patients had persistently elevated PVR. In the patients with adequately controlled pulmonary hypertension, postoperative outcomes were virtually identical to those patients without pulmonary hypertension. There was a significant difference in mean length of intubation (1.2 vs 19.5 days, P=0.02) and mean postoperative length of stay (9.4 vs 27 days, P=0.05) compared to untreated patients. Four of the treated patients were able to stop oral pulmonary vasodilators on day of transplant; the remaining 3 continue on treatment with PVR ranging from 2.2-4.3 WU. The 2 patients with persistently elevated PVR at time of transplant, as well as 3 of the untreated pulmonary hypertensives, suffered acute pulmonary hypertensive crises requiring prolonged ventilatory and circulatory support. The three of the patients with untreated pulmonary hypertension were treated for episodes of rejection within the first year, and 2 of those patients died; 2 patients without pulmonary hypertension experienced episodes of rejection with 1 death. In conclusion, aggressive treatment of altered pulmonary hemodynamics promotes favorable outcomes in children with restrictive cardiomyopathy undergoing heart transplant.