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SYSTEMIC ENDOTHELIAL DYSFUNCTION IN CHILDREN WITH IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION CORRELATES WITH DISEASE SEVERITY

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Abstract

Background—Idiopathic pulmonary arterial hypertension (IPAH) is a life-threatening disease manifested by progressive pulmonary vascular remodeling, compromised pulmonary blood flow and right heart failure. Most studies explore how pulmonary endothelial function modulates disease pathogenesis. We hypothesize that IPAH is a progressive panvasculopathy, affecting both pulmonary and systemic vascular beds, and that systemic endothelial dysfunction correlates with disease severity. Recent studies demonstrate systemic endothelial dysfunction in adults with pulmonary hypertension, however adults often have additional comorbidities affecting endothelial function. Systemic endothelial function has not been explored in children with IPAH.

Methods—This single-center, prospective, cross-sectional study examined brachial artery flow mediated dilation (FMD), a nitric oxide mediated, endothelial-dependent response, in children with IPAH and matched controls. FMD measurements were compared with clinical and echocardiographic measures of IPAH severity.

Results—Thirteen patients and 13 controls were studied, ages 6–20 years old. FMD was decreased in IPAH subjects compared with controls (5.1 $\pm$ 2.1% vs 9.7 $\pm$ 2.0%; $p < 0.0001$). In IPAH subjects, FMD correlated directly with cardiac index ($R^2 = 0.34$, $p = 0.035$), and inversely with tricuspid regurgitation velocity ($R^2 = 0.57$, $p = 0.019$) and right ventricular myocardial performance index ($R^2 = 0.44$, $p = 0.028$).

Conclusions—The presence of systemic endothelial dysfunction in children with IPAH and its strong association with IPAH severity demonstrate that IPAH is a global vasculopathy. Although morbidity in IPAH is typically associated with pulmonary vascular disease, systemic vascular changes may also relate to disease pathogenesis and progression. Further study into shared mechanisms of systemic and pulmonary endothelial dysfunction may contribute to future therapies for IPAH.

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INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive vasculopathy characterized by restricted blood flow through the pulmonary arterial circulation, elevated pulmonary vascular resistance (PVR) and eventual right heart failure¹. The prevalence of IPAH is approximately 6 per million overall^{1, 2} and 2 per million children³. Mortality in IPAH is generally secondary to progressive right heart failure and inadequate cardiac output^{1, 4, 5}, although sudden death occurs in a subset of patients^{4, 6}. Despite improvements in treatment over the past few decades, mortality from IPAH remains high^{1, 7}.

The pathogenesis of IPAH involves dysregulation of pulmonary vascular endothelium, manifested by (1) excessive proliferation and inhibited apoptosis of vascular smooth muscle cells and (2) an imbalance in the expression of endogenous vasoconstrictors (e.g. endothelin, thromboxane) and vasodilators (e.g. nitric oxide (NO), prostacyclin), favoring expression of vasoconstrictors. Current therapies focus on promoting vasodilatation and inhibiting pathologic remodeling in the pulmonary vascular bed.

Research into the pathophysiology of IPAH has generally focused on the pulmonary vasculature. However, IPAH patients have elevated circulating levels of vasoconstrictors, suggesting that the disease process may not be limited to the pulmonary vascular bed^{8–10}. There has been limited evaluation of the systemic vasculature in this disorder. Impaired systemic endothelial function has been identified in patients with risk factors for cardiovascular disease. It is also an independent predictor of poor outcomes in patients with coronary artery disease or chronic left heart failure^{11–15}. The most commonly used non-invasive method of analyzing systemic endothelial function is brachial artery flow mediated dilation (FMD). FMD is a measurement of the nitric-oxide (NO)-dependent vasodilatation of the brachial artery in response to shear stress from temporary restriction to blood flow and reperfusion. Because of its dependence on NO, which is depleted in both the pulmonary vascular bed¹⁶ and the systemic circulation¹⁷ in patients with IPAH, we hypothesized that FMD may be impaired in these patients. There have been no studies to date evaluating systemic endothelial function in children with pulmonary hypertension.

The purpose of this study was to evaluate systemic endothelial function in a population of children with IPAH. We hypothesized that IPAH is a progressive panvasculopathy, affecting both the pulmonary and systemic vascular beds, and that children with IPAH would have impaired FMD compared with healthy controls, and proportional to their IPAH severity.

METHODS

Subject recruitment

All patients followed at our institution for a diagnosis of IPAH were considered for inclusion in this prospective, cross-sectional study. All charts were reviewed to obtain history, including prior catheterization data, and to confirm eligibility for inclusion. Patients under five years of age were excluded based on their inability to cooperate with the study protocol. Additional exclusion criteria included a history of any of the following: intrinsic airway or pulmonary parenchymal disease, including significant reactive airway disease; connective tissue disease; hemoglobinopathy; systemic vasculopathy; cardiomyopathy; or large intracardiac shunt lesion. Patients with only a small atrial septal defect or a small patent ductus arteriosus were not excluded. Fourteen patients met study inclusion criteria, and all consented to participate. One patient was later excluded due to inability to cooperate with study protocol requirements.

A group of thirteen healthy control subjects was recruited through advertisement by the cardiologists at our institution. Controls were age-matched within 1 year of study subjects and gender-matched. All control subjects had no significant past medical history, were on no medications, and had normal cardiac anatomy and function on echocardiogram at the time of participation. All study participants denied any alcohol or illicit drug use or cigarette smoking.

The study protocol was approved by the Children's Hospital Los Angeles institutional review board, and Informed consent was obtained for all subjects prior to data collection.

Data Collection and Analysis

All subjects were instructed to refrain from any food or drink, except as required for medication administration, for at least 6 hours prior to their study visit, and to refrain from caffeine intake for at least 24 hours. Subject's height, weight and vital signs were collected at the start of the study visit. All studies were conducted in a quiet, dimly lit room. Echocardiography was typically performed first, followed by brachial artery FMD analysis. Subjects were placed either supine or on their left side for echocardiography and supine with head elevated 30 degrees for FMD analysis. After all ultrasound studies were completed, IPAH patients performed six-minute walk tests under standardized conditions per our PAH clinic protocol. In all but three subjects, the echocardiogram, FMD and walk test were performed at the same visit. However, in three cases where technical issues necessitated repeating FMD analysis, no more than 3 months transpired between echocardiography and FMD. Within that interim, there were no changes in subject's medication regimen, clinical status, or TR velocity.

All echocardiograms were performed on a Philips IE33 echocardiography machine, using standard 5 and 8 MHz sector array transducers. Complete echocardiography studies were performed with 2-D, and color, spectral and tissue Doppler imaging. Apical 4-chamber view was used for tissue Doppler analysis of mitral and tricuspid annular excursion and pulse-wave Doppler assessment of mitral inflow and aortic outflow. Left ventricular outflow tract (LVOT) diameter was measured from parasternal long axis images. Cardiac output was estimated using LVOT velocity time integration (VTI), and right ventricular (RV) and left ventricular (LV) myocardial performance indices (MPI) were measured using tissue Doppler technique at the lateral mitral and tricuspid valve annuli. All Doppler measurements were performed on three heartbeats and averaged. Continuous wave Doppler assessments of tricuspid regurgitation velocity were performed in all views, and the maximal velocity obtained was used to estimate systolic pulmonary artery pressures, without correction for right atrial pressure.

Assessment of brachial artery flow mediated dilation (FMD) was performed according to standard protocols as reported by Peretz et. al.¹⁸. An appropriately sized, manual blood pressure cuff with sphygmomanometer (Welch Allyn inc. model#DS66) was placed on the forearm. Using a Philips IE-33 ultrasound system, a linear ultrasound probe (L-9, Philips Medical Systems) was used to measure baseline brachial artery diameter 1–2cm proximal to the antecubital fossa, prior to cuff inflation. The cuff was then inflated to 50mmHg above systolic blood pressure for five minutes occluding blood flow to the distal extremity. At least two measurements of brachial artery diameter were made during occlusion. After five minutes, the cuff was deflated, and 20-second ultrasound clips of the brachial artery were obtained continuously for an additional 5 minutes. Analysis of brachial artery diameter was performed using automated software designed for FMD analysis (Brachial Artery Analyzer version 5.0, Medical Imaging Applications inc, Coralville, Iowa) and reviewed manually. The pre-inflation diameter and maximal diameter post-deflation were used for FMD calculations. All analyses were independently performed and reviewed by two researchers

who had been trained in FMD analysis, one of whom was blinded to subject class. Bland-Altman analysis demonstrated no significant inter-observer bias [-0.28 ; 95% confidence interval -0.79% to 0.23%], therefore FMD results were averaged.

Statistical Analyses

Two-tailed Student's T-tests were used to compare baseline characteristics and FMD between patients and control subjects. Bland-Altman plots were used to describe interobserver agreement on FMD analyses. Linear regression analyses were conducted to assess relationships between FMD and various echocardiographic measures of RV and LV size and function. All statistical analyses were performed using JMP 9 statistical software (SAS, Cary, North Carolina).

RESULTS

13 IPAH patients and 13 control subjects were included in the analysis. Data collection, including echocardiography and assessment of brachial artery FMD was complete in all subjects. In addition, all IPAH patients completed a six-minute walk test. There were no significant differences in the demographics or baseline blood pressures between the two groups (Table 1). Mean heart rate was higher in the group with IPAH ($p=0.014$), likely reflecting a compensatory response to maintain adequate cardiac output in the face of lower stroke volume secondary to high RV afterload.

IPAH subjects were on various medication regimens for their pulmonary hypertension, based on the length and severity of their illness and the preferences and experiences of their treating physician. Table 2 shows the baseline characteristics of the IPAH patients and the various medications they were being treated with at the time of data collection. Of note, one patient was newly diagnosed, and her only treatment at the time of data collection was oxygen.

Shear mediated nitric oxide responsiveness was assessed by brachial artery FMD (Figure 1). FMD response was markedly attenuated in children with IPAH compared with control subjects ($5.1\pm 2.1\%$ vs $9.7\pm 2.0\%$; $p<0.0001$). As shear stress is inversely related to vessel diameter, we compared baseline brachial artery diameters between the two groups and found no difference (Table 1).

FMD was then compared with echocardiographic markers of IPAH severity. Figure 2 demonstrates a negative correlation between FMD and tricuspid regurgitation (TR) velocity in children with IPAH ($R^2=0.57$, $p=0.019$). TR jets with incomplete envelopes are indicated by black circles and were excluded from correlation analysis. TR velocities for control subjects are shown for comparison purposes (gray diamonds); however, these data were not included in the correlation.

FMD was also inversely related to RV MPI ($R^2=0.44$, $p=0.028$), a quantitative assessment of global RV function (Figure 3). RV MPI correlates with the reciprocal of FMD and worsens dramatically as FMD falls below approximately 5%. LV MPI, as a quantitative measure of global LV function, was significantly higher in IPAH patients compared to controls (0.55 ± 0.12 vs 0.38 ± 0.05 ; $p<0.001$), but was independent of FMD.

Cardiac index correlated linearly with FMD ($R^2=0.34$, $p=0.035$), consistent with FMD's association to RV pressure and RV function (Figure 4). Clinical markers of PAH severity, six-minute walk distance and World Health Organization (WHO) classification, did not demonstrably correlate with TR velocity, cardiac index, or FMD.

DISCUSSION

In this study, we demonstrate that systemic endothelial function is impaired in pediatric patients with IPAH. This is the first study evaluating the systemic vasculature in children with this disease, and our findings validate and uniquely broaden the findings of previous studies. Several groups recently showed evidence of systemic endothelial dysfunction in adults with various types of pulmonary hypertension^{19–22}. However, there are several clinical and histopathological differences between pediatric and adult IPAH⁷. Therefore, there may be physiologic differences as well, and it may be incorrect to extrapolate from adult data to pediatric patients with respect to systemic endothelial function. Furthermore, given the demographics of the patients in the adult studies, it is difficult to exclude typical cardiovascular risk factors as contributing to impaired endothelial function. Atherosclerosis²³, diabetes^{24, 25}, hypertension²⁶, obesity²⁵, hypercholesterolemia²⁵, and cigarette smoking²⁷ are all known to impact systemic endothelial function and FMD measurements. Although an adult PAH population may demonstrate these risk factors in proportion to healthy adults¹⁹, it may be difficult to identify all individuals with subclinical disease. Children, however, typically do not have these comorbidities. The demonstration of impaired systemic endothelial function in a pediatric IPAH population indicates that the pathophysiology of IPAH is not limited to the pulmonary vascular bed, and that the systemic vasculature is impacted as well. However, our study cannot distinguish whether systemic endothelial dysfunction represents systemic manifestations of a broader vasculopathy process or secondary changes in response to decreased cardiac output.

The exact mechanism underlying endothelial dysfunction in IPAH is unclear. Impaired endothelial function in the pulmonary vascular bed has long been known to be an integral element in the pathogenesis of IPAH^{1, 28}. This dysfunction is in part characterized by altered expression of endogenous vasodilators (NO, prostacyclin) and vasoconstrictors (endothelin, thromboxane) in the lung vascular bed^{16, 29}. There have been several studies showing elevated serum levels of vasoconstrictors in PAH patients^{8–10}, and plasma levels of nitric oxide are reduced¹⁷. Additionally, circulating levels of asymmetrical dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthase, are increased in patients with pulmonary hypertension^{30–32}. Therefore, it is unsurprising that systemic endothelial function, and in particular FMD, a nitric-oxide dependent response, is compromised in patients with IPAH. Future studies would measure NO and ADMA levels in our patients to evaluate whether they correlate with the degree of endothelial dysfunction.

The second major finding of this study is that systemic endothelial dysfunction in children with IPAH correlates with echocardiographic measures of disease severity, including estimated pulmonary artery pressures, RV function and cardiac output. While the interpretation of RV MPI values remains controversial, it is being increasingly used as a quantitative measure of RV function, and the strength of our correlation supports a meaningful relationship between endothelial and RV function.

Interestingly, clinical markers of PAH severity, including WHO class and 6-minute walk distance, did not correlate with FMD or with any of the echocardiographic measures of IPAH severity. Besides relating to sample size, this may reflect the fact that these clinical measures are less reliable in young children^{7, 33}. Children with IPAH have similar pulmonary vascular pathology compared to adults, but they have more aggressive disease and poorer outcomes^{1, 7, 34, 35}. Prediction of disease progression can be more difficult in pediatric subjects than in adults. Traditional predictors of poor prognosis in PAH include: advanced WHO functional class, poor exercise capacity, high right atrial pressures, RV failure, and low cardiac index¹. These parameters can be difficult to monitor in children, who may be less cooperative with medical history-taking, exercise testing, or six-minute-

walk testing^{7, 33}. Furthermore, children with PAH may initially be physiologically better compensated with severely elevated pulmonary resistance compared to adults^{1, 7}, making an immediate determination of prognosis difficult. Therefore, hemodynamic parameters remain critical for assessment of disease severity in pediatric PAH patients⁷, and our findings suggest that FMD may provide an additional, objective method for evaluating disease severity in this patient population. There is evidence in adults that FMD correlates with acute improvements in pulmonary vascular reactivity to inhaled prostacyclin¹⁹. However, the relationship between systemic endothelial dysfunction and IPAH progression, morbidity and response to treatment remains to be determined, particularly in children.

There are several limitations to this study. There are technical challenges to obtaining quality FMD measurements, particularly in young children who may have difficulty remaining still for the duration of image acquisition. However, with parental assistance, reliable ultrasound images were obtained in children as young as six years old. Young children also have smaller vessels than older subjects, increasing the relative difference in FMD calculations. Despite measurement variability and the small sample size, there was little overlap in FMD between patient and control groups and correlation between FMD and echocardiographic metrics was quite good.

Our small sample size, and the lack of standardization in our patients' medication regimens are also significant limitations that might be addressed in larger future studies. Several medications used for IPAH may affect systemic vascular tone and FMD along with their effects on the pulmonary vasculature. However, we found no difference in the baseline brachial artery diameter between patients and controls (table 1), nor was there a difference between patients on and off IV therapy (data not shown), suggesting that PAH medications did not result in a dilated baseline state. Ideally, one would study the relationship between FMD and pulmonary hypertension in IPAH patients prior to and following initiation of standardized therapy; however, we could not ethically alter patient medications for this study.

Finally, the absence of any correlation with invasive measurements of pulmonary pressures is a significant limitation to this study. Standard of care at our institution, as at many other pediatric PAH centers, is for children with IPAH to undergo cardiac catheterization only at the time of diagnosis. Echocardiographic windows and image quality are generally superior in children compared with adults, and hemodynamic estimates are quite reproducible. Therefore, our patients are routinely followed with non-invasive testing only, unless a new issue arises that necessitates repeat catheterization. Available catheterization data for study patients were not included as, in many cases, the data were over five years old and not necessarily representative of the patient's current hemodynamic state.

In conclusion, this study suggests that IPAH is a panvasculopathy and that systemic endothelial dysfunction is a fundamental component of the disease process. This is the first study to demonstrate a relationship between systemic vascular function and pediatric IPAH as well as its correlates with disease severity. Longitudinal studies are ongoing to assess whether systemic endothelial dysfunction is associated with disease progression, response to medical therapy, and outcomes in our patient population. Larger, multi-institutional trials will be necessary to further explore the mechanisms and consequences of systemic endothelial dysfunction in this population.

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Figure 1. FMD is significantly reduced in children with IPAH compared with control subjects. Shorter lines represent mean and standard error of the mean. Longer lines represent standard deviation

Figure 2.

FMD is inversely related to tricuspid regurgitation (TR) velocity. TR velocity (v) is related to RV pressure (p) by the formula $p=4v^2$. Fit line includes patients only. Circles represent studies with incomplete Doppler envelopes and were excluded from fit.

Figure 3. Right ventricular myocardial performance index (MPI) is inversely related to the reciprocal of FMD, indicating that RV function worsens dramatically as FMD falls below approximately 5%. Controls excluded from fit

Figure 4.
Cardiac index increases linearly with FMD. Controls excluded from fit.

Table 1

Baseline demographics

	PATIENTS	CONTROLS	p-value
Age (years)	11.5 ± 5 [6–20]	11.5 ± 3.9 [6–19]	0.98
Percent Male (n)	21.4 (3)	7.7 (1)	0.3
Weight (kg)	42.5 ± 23.4 [18–91.6]	44.9 ± 21.4 [20–79]	0.78
Body mass index (kg/m²)	20.3 ± 5.9 [13.7–32.4]	19.7 ± 5.6 [13.8–30.6]	0.81
Heart rate (beats per minute)	87.9 ± 16.4 [62–120]	73.3 ± 11.8 [63–89]	0.014
Systolic BP* (torr)	104.6 ± 11.2 [93–123]	108.9 ± 11.9 [94–132]	0.337
Diastolic BP* (torr)	60.5 ± 10.43 [42–87]	60.4 ± 8.51 [50–78]	0.975
Baseline brachial artery diameter (mm)	2.82 ± 0.93 [2.6–4]	2.69 ± 0.32 [2.2–3.4]	0.62

Values given as mean ± standard deviation [range] unless otherwise indicated.

* BP = Blood Pressure

Table 2

Baseline characteristics of IPAH patients, n=13

WHO class (I–IV)	1.7 ± 0.9 [1–4]
Baseline saturation (%)	97.1 ± 2.7 [93–100]
Estimated PA[*] pressure (torr)	85.5 ± 30.2 [44–140]
6 minute walk distance (meters)	355 ± 68 [276–449]
Medications, number of subjects (%)	
Phosphodiesterase Inhibitor	6 (46%)
Endothelin Receptor Antagonist	7 (54%)
IV Prostacyclin	4 (31%)
Inhaled Prostacyclin	2 (15%)
Diuretics	4 (31%)
Coumadin	5 (38%)
Aspirin	3 (23%)
24 hour oxygen	4 (31%)
Oxygen overnight and prn	8 (62%)

Values given as mean ± standard deviation [range] unless otherwise indicated.

* PA = Pulmonary artery