Advances in Pulmonary Hypertension

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PH in Congenital Heart Disease

Atrial Septal Defect–Associated Pulmonary Hypertension: Outcomes of Closure With a Fenestrated Device *Vishal Kaley, MD; Nagib Dahdah, MD; Amal El-Sisi, MD et al.*

Challenges in the Patient With Pulmonary Hypertension and Atrial Septal Defect: Understanding When and How to Close the Defect *Mary P. Mullen, MD, PhD*

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PH Professional Network: Comprehensive Evaluation and Ongoing Approach to Children With Down Syndrome Who Have Pulmonary Hypertension or Are at Risk of Developing Pulmonary Hypertension *Emma Olson Jackson, NP; Anne Davis, RN*

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The mission of Advances in Pulmonary Hypertension is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2018 Nice revision of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed in Advances in Pulmonary Hypertension. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, PH due to pulmonary artery obstructions; Group 5, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

 Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.

· Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of Advances in PH is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
 Letters to the Editor
- Letters to the Editor
 Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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Advances in Pulmonary Hypertension is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

Benefits of Registration Include:

- A unique user profile that will allow you to manage your current subscriptions (including online access)
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Welcome to the first issue of Advances in Pulmonary Hypertension Volume 18. As I transition to the role of editor-in-chief, I look forward to taking part in this incredible effort with our PHA Advances staff, editorial board (Harrison Farber, MD; Sean Studer, MD, MSc; Marc Humbert, MD, PhD; Jeffrey D. Edelman, MD; Dunbar Ivy, MD; Richard Krasuski, MD; Ioana R. Preston, MD; Traci Housten, RN, MS; Anna R. Hemnes, MD; Usha Krishnan, MD; Nick Morrell, MD, ScD, FMedSci; Jonathan D. Rich, MD; John J. Ryan, MD, FACC, FAHA; Oksana A. Shlobin, MD; Anjali Vaidya, MD, FACC, FASE, FACP), and guest editors to continue the quality work that has been delivered over the last two decades. 2019 is an important year for scientific topics in Advances as we continue the momentum that Dr Farber initiated during his tenure as editor-in-chief. The expert-led issues will include coverage of congenital heart disease, imaging, exercise and PH, and the 6th World Symposium on Pulmonary Hypertension.

I would like to thank and congratulate Dr. Harrison Farber for his solid leadership of our editorial board over the past two years. His exhaustive knowledge of our field and the insight on how to best navigate each issue led to the publication of eight excellent issues covering important current topics in PH. I look forward to his continued guidance and his innate ability to bring a smile to every conversation over the next two years. I would also like to thank the editorial board members for all of the time and effort toward making each issue an important addition to the PH literature and to our patients' lives. Thank you to PHA and the *Advances* staff for their solid commitment and dedication to the focus of this important journal. And to Deborah McBride, our managing editor for the last nine years, a very special heartfelt thank you for all of the devotion, generosity, and hard work you have provided us to make it all happen. Your support has been invaluable. You have touched us all.

The new year brings exciting developments in how information in Advances will be delivered to us. Similar to many other scientific journals, Advances will transition its format to an online-only journal. By transitioning to a new online platform, the journal offers the PH community enhanced access to the information, and an opportunity to reach and benefit a wider audience. We encourage readers to register on the site to receive announcements about updates and to be able to take advantage of all the features the new platform offers. The focus of this journal will not change. It will continue, as it has for the last 17 years, to deliver up-to-date valuable peer-reviewed knowledge dedicated to clinicians, scientists, and those in training on the complicated topic of PH.

In this issue, we examine the complicated topic of congenital heart disease

(CHD) and PH. I want to congratulate and thank Dr Dunbar Ivy (our guest editor) and Dr Hap Farber for assembling a world-class group of contributors to focus on this difficult subject. This topic truly reflects the idea that evaluating and managing our patients is a team-based, complicated, multispecialty process. Advances in therapies continue to improve for patients with CHD, making it possible for children to live well into adulthood. Complications, however, from both CHD and PH still require the input from a multitude of specialists working together to improve survival and quality of life. This issue of Advances is a valuable resource that provides original research; current reviews on the evaluation, management, and future options of patients with CHD and PH; and an important roundtable discussion on CHD management.

I look forward to working with our *Advances* team over the next two years as editor-in-chief with the goal of bringing the quality education, research updates, and current discussions to all of our readers in hopes of improving our patients' lives.

Deborah Jo Levine, MD

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GUEST EDITOR'S MEMO

For this issue of *Advances in Pulmonary Hypertension* we are focusing on pulmonary hypertension in congenital heart diseases in child and adult. Treatment of these patients is challenging due to the lack of randomized trials. Medications used in congenital heart disease patients are rarely studied as a prospective cohort study, but rather as part of other clinical trials in Group 1 PH (PAH). This issue is dedicated to the crossover between the adult and child with pulmonary hypertension and congenital heart disease. Several important gaps are recognized between our knowledge and treatment of adults and children. These are readily apparent in the guidelines, which have been published recently by the European Respiratory Society, as well as in the journal *Circulation*. The adult guidelines include very strict criteria for operability. These criteria discourage a treat-and-repair approach, where the patient would be treated with medication and then undergo a repeat catheterization and then a reconsideration of cardiac defect closure. In contrast, in the pediatric guidelines, there is a potential for a treat-and-repair strategy, where patients who would not be classically operable could be treated and then reconsidered for surgical operability. Another key issue is the growing number of older children and adults with a single ventricle circulation or palliation. In these patients, a small rise in pulmonary vascular resistance may lead to circuit failure. In the classic sense, these patients do not meet the criteria for PH of an increase in mean pulmonary artery pressure, but they do have circuit failure due to an increase in pulmonary vascular resistance. I am grateful to the authors of the articles in this issue and to those participating in the robust roundtable discussion.

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Atrial Septal Defect–Associated Pulmonary Hypertension: Outcomes of Closure With a Fenestrated Device

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Unlike other intracardiac shunts, there is no known linear relationship between ostium secundum atrial septal defects (ASD) and development of pulmonary hypertension (PH). PH is observed in 8% to 10% of all ASD patients. Atrial septal defect–associated pulmonary hypertension (ASDAPH) is usually independent of the degree, duration of shunting, and defect size. Complete closure of ASD in these patients can be detrimental due to the potential risk for increase in pulmonary vascular resistance (PVR). Fenestrated closure allows for controlled residual shunt providing adequate cardiac output with a mechanism for decompression in the event of critical increase in PVR. After approval from institutional review boards and agencies protecting human subjects, 42 patients from 29 international centers underwent compassionate use of the Occlutech[®] Fenestrated Atrial Septal Defect (FASD) device. Physician implanters reported outcomes via electronic survey. Follow-up data were available for 25 patients (72% female, n=18) from 18 centers. Symptomatic improvement was observed in a majority of the patients with reduction in New York Heart Association class III symptoms from 68% at baseline to 8% at long-term follow-up. Mean oxygen saturation improved from 93% at baseline to 97% at long-term follow-up (*P*=0.0066). Reduction in right atrial pressure and mean pulmonary arterial pressure were also noted. During follow-up, one patient had spontaneous occlusion of the fenestration requiring emergency stenting. No other major complications were observed. FASD implantation improves outcomes in patients with ASDAPH; however, further studies are required in a large cohort of patients to determine timing of intervention, optimal fenestration size, and long-term prognosis.

Key Words—atrial septal defect, atrial septal defect–associated pulmonary hypertension, congenital heart disease, fenestrated defect closure, interventional cardiology, pulmonary arterial hypertension Correspondence: joseph.vettukattil@helendevoschildrens.org

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Atrial septal defect (ASD) is a common congenital heart defect (CHD) with a worldwide incidence of 1.64 per 1,000 live births.¹ Ostium secundum ASD is the most prevalent type accounting for 70% to 80% of all cases. The absence of major clinical symptoms and physical findings can lead to delayed diagnosis; as such, ASDs are often diagnosed in adulthood.² Approximately 8% to 10% of patients with ASD can develop pulmonary hypertension (PH), a severe chronic condition with progressive increase in right ventricular (RV) pressure and pulmonary vascular resistance (PVR), associated with secondary right heart failure, and high mortality rates.³ Patients with untreated CHD have higher risk for developing PH.³ CHDs characterized by high pulmonary pressures and/or high pulmonary flow states are more commonly known to develop reversal of shunting and cyanosis known as Eisenmenger's syndrome.⁴ However, there is no known linear relationship between PH and ASDs and the pathogenic mechanism is unknown.⁵

A subset of patients with ASD may develop severe PH at an earlier age. This atrial septal defect-associated pulmonary hypertension (ASDAPH) is more common in females accounting for around 85% of all observed cases. ASDAPH often presents in the second or third decade of life and is typically independent of the degree of shunting.^{6,7} ASDAPH has better prognosis than idiopathic PH possibly due to right-to-left shunting preventing cardiovascular collapse and syncope during critical increase of PVR.8 However, outcomes on medical therapy in ASDAPH are unreliable with worsening of symptoms in the majority of patients despite multiple drug therapy.⁸

Although transcatheter or surgical repair of ASDs with normal mean pulmonary arterial pressure (MPAP) is considered safe and widely accepted procedure with negligible mortality, there are no specific techniques or established guidelines for the treatment of AS-DAPH.^{9,10} Complete closure of the defect in ASDAPH by transcatheter or surgical approach may result in complications associated with sudden increase in PVR.¹¹⁻¹⁴

The concept of fenestrated closure is to keep a residual shunt, which acts as a decompression mechanism, and



Figure 1: The Occlutech[®] Fenestrated Atrial Septal Defect device.

maintains adequate cardiac output in the event of critical increase in PVR.¹³⁻¹⁵ Various improvisations in transcatheter and surgical closure have been attempted without significant success.^{16,17} This led to the development of a novel transcatheter closure device, the Occlutech[®] Fenestrated Atrial Septal Defect (FASD) device.^{18,19} We report outcomes of FASD device implantation in ASDAPH.

MATERIALS AND METHODS

Patients with ASDAPH refractory to medical therapy underwent compassionate use of FASD device approved by institutional review boards and agencies protecting human subjects. The outcomes were reported via electronic survey by physician implanters from 18 centers. Patients with moderate to large ASDs with adequate margins were considered suitable for implantation.

Device and Delivery System

The FASD device consists of a nitinol (51% nickel, 49% titanium) wire mesh (Figure 1). A flexible waist with a fenestration connects the 2 retention discs corresponding to the size of the ASD, which completely conforms to the atrial septum after deployment. Two very thin polyethylene terephthalate patches ensure faster sealing of the ASD while optimizing endothelialization for a sustainable atrial communication. The devices are available in 3 fenestration sizes with a proprietary delivery system based on the device diameter (Table 1).

Device Deployment

Pre-deployment transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) were performed

Table 1. Fenestrated Atrial Septal Defect

 Device Fenestration Size and Delivery System

Fenestration size (mm)	Device	Delivery system (F)				
5	25ASD15F	11				
	25ASD18F, 25ASD21F	12				
6	25ASD24F	12				
	25ASD27F, 25ASD30F	14				
8	25ASD33F, 25ASD36F, 25ASD40F	14				
	25ASD44F, 25ASD48F	16				

to confirm the anatomy and margins of the ASD. The appropriate device and fenestration size for individual patients were determined based on the pre-deployment cardiac catheterization data including balloon sizing. The patients underwent transcatheter FASD implantation via femoral vein access under fluoroscopic and TEE guidance (Figure 2).

Patient Follow-up

Follow-up visits were defined as shortterm if they occurred between 1 and 6 months and long-term if they occurred between 6 and 12 months after the procedure. Clinical parameters (New York Heart Association [NYHA] functional class, 6-minute walk test [6MWT], and oxygen saturation), echocardiographic outcomes (device position, patency, and direction of shunting), and catheterization data were collected during follow-up.

Statistical Analysis

Data were analyzed using Statistical Analysis Software (Version 9.4, SAS Institute, Inc., Cary, NC). Numerical data were expressed as mean and standard deviation or median and range. A paired t-test and ANOVA were performed to compare pre- and post-deployment changes. A *P* value of <0.05 was considered to be significant for differences between parameters.

RESULTS

Patient Characteristics

Forty-two patients underwent transcatheter FASD implantation at 29 international centers. Complete pre- and post-procedural data were available for 25 patients from 18 centers (Table 2). The majority of patients were adults (84%, n=21/25) with median age of 60 years (range 5 to 80 years). Female preponderance was noted (72%, n=18/25). Based on NYHA class, patients were considered severely symptomatic if they had either NYHA class III or IV symptoms; 68% of patients had NYHA class III symptoms (n=17/25), the remaining 32% (n=8/25) had class II symptoms. 6MWT was used to assess the aerobic capacity and endurance of the patients. Severely symptomatic and bedridden patients (n=4) who could not complete



Figure 2: Post-deployment 3D TEE shows a well-seated FASD device in the interatrial septum with a patent fenestration.

the 6MWT were not included in the statistical analysis. The mean baseline 6MWT distance was 228±183 meters for 14 patients who completed the test. The mean oxygen saturation prior to implantation was 93±4% (n=25) ranging from 88% to 100%.

On pre-deployment TTE and TEE, patients were noted to have ASDs ranging in sizes from 15 to 40 mm. It was observed that 63% of patients (n=12/19) had bidirectional or right-to-left shunting across the fenestration. Baseline mean left atrial (LA) and right atrial (RA) pressures were noted to be 13±4 mm Hg and 12±3 mm Hg, respectively. The MPAP was 46±19 mm Hg. All patients were receiving anti-PH medications, with 20% on dual drug therapy (Table 2). All patients were on anticoagulants and antiplatelet agents alone or combination therapy for variable duration (range 6 weeks to 6 months) depending on the individual institutional protocols.

Deployment

All patients (n=25) underwent successful implantation on the first attempt. No deployment-related complications were reported in any of the patients. The im-

Table 2. Patient Demographics

Age (years)	51 (5-80)				
Gender (female)	18/25 (72.0%)				
Height (cm)	155±19				
Weight (kg)	70±24				
Systemic systolic pressure (mm Hg)	122±16				
Systemic diastolic pressure (mm Hg)	68±9				
Mean arterial pressure (mm Hg)	86±9				
Procedure time (minutes)	76±44				
Fluoroscopy time (minutes)	13±11				
PH medical therapy					
None	1/25 (4.0%)				
Dual	5/25 (20.0%)				
Triple	19/25 (76.0%)				
Implanted AFR device fenestration size					
5 mm	5/23 (21.7%)				
6 mm	13/23 (56.5%)				
8 mm	5/23 (21.7%)				

Table 3. Change in Pa	rameters Following I	FASD Implantation
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Parameters	Baseline	Short-term follow-up	Long-term follow-up	P value
O ₂ saturation at rest (%)	93±4 (n=25)	96±3 (n=22)	97±2 (n=12)	0.0066 (n=12)
O_2 saturation after exercise (%)	88±7 (n=7)	84±31 (n=9)	75±41 (n=5)	t
6MWT distance (m)	228±183 (n=14)	351±179 (n=12)	457±83 (n=5)	0.0081 (n=12)
NYHA functional class	n=27	n=23	n=12	
I	0 (0%)	7 (30.43%)	8 (66.7%)	
II	8 (32.0%)	13 (56.5%)	3 (25.0%)	
III	17 (68.0%)	3 (13.0%)	1 (8.3%)	
IV	0 (0%)	0 (0%)	0 (0%)	
RA pressure (mm Hg)	12±3 (n=24)	10±3 (n=17) [‡]	8±4 (n=5)	0.0502 (n=17)
LA pressure (mm Hg)	13±4 (n=23)	14±4 (n=16) [‡]	11±1 (n=4)	0.9252 (n=16)
MPAP (mm Hg)	46±19 (n=24)	42±17 (n=17) [‡]	42±22 (n=5)	0.0004 (n=17)

†Due to low n and high standard deviations for short- and long-term, only descriptive statistics are given. ‡Represents cardiac catheterization data from the immediate post-deployment period.

planted FASD devices had fenestration sizes of 5 mm (n=5), 6 mm (n=13), and 8 mm (n=5) with device size ranging from 15 to 40 mm. The mean procedural time was 76 minutes with mean fluoroscopy time of 13 minutes (range 6 to 34 minutes). Immediate post-deployment TEE confirmed optimal device position and patency of the fenestration in all the patients.

Follow-up

Of the 25 patients included in the study, 23 completed short-term follow-up, and 12 completed long-term follow-up (Table 3). Significant symptomatic improvement was observed in the majority of patients following FASD deployment. NYHA class III symptoms were observed in 13% of patients (n=3/23) at short-term follow-up and in 8% (n=1/12) at long-term follow-up as compared to 68% patients prior to FASD device implantation. One patient who had atrial fibrillation and was being medically treated experienced symptomatic improvement and was found to be in sinus rhythm on follow-up electrocardiogram. The mean oxygen saturation improved from baseline of 93±4% to 96±3% (n=22, P=<0.0001) at short-term follow-up and 97±2% at long-term follow-up (n=12, P=0.0066). There was significant improvement in the endurance level of patients evident from improvement in 6MWT distance from

228±183 meters to 351±179 meters at short-term follow-up (n=12, *P*=0.0081), and 456±83 meters at the long-term follow-up (n=5). Follow-up TTE demonstrated optimal position and patent fenestration in all patients at short-term follow-up. The TTE also demonstrated RV remodeling and it was observed that 78% patients (n=7/9) had left-to-right shunting across the fenestration with obvious decrease in RV size.

As cardiac catheterizations were performed in only 5 patients at long-term follow-up, the data were not suitable for statistical analysis and comparison with baseline data. Instead the immediate post-deployment catheterization data (n=17) were used for comparison and calculation of the P value. Cardiac catheterization showed expected, but trivial decrease in RA pressure from 12±3 to 10±3 mm Hg (n=17, *P*=0.052) immediately after deployment, and a substantial decrease to 8±4 mm Hg (n=5) at long-term follow-up. The LA pressure remained unchanged at 14±4 mm Hg (n=16, P=0.9252) in the immediate post-deployment assessment and decreased from 13±4 to 11±1 mm Hg at long-term follow-up (n=4). A significant decrease in mPAP was noted from 46±19 to 42±17 mm Hg immediately after deployment (n=17, P=0.0004) and to 42±22 mm Hg at long-term follow-up (n=5). At short-term follow-up, all patients continued anti-PH medication therapy. At long-term follow-up one patient had the fenestration closed with an ASD occluder device in view of symptomatic improvement, normalized mPAP, and hemodynamics. Post-implantation symptomatic improvement and normalization of the rhythm was observed in one patient with atrial fibrillation.

Complications

All patients had uneventful device deployment with no deployment-related complications. One patient developed pseudoaneurysm with an arteriovenous fistula at the catheterization site requiring thrombin injections. No device-related complications were observed except in one patient on aspirin therapy who was observed to have worsening of symptoms on follow-up and had the 24 mm FASD device with 6 mm fenestration. On subsequent evaluation, TTE revealed complete occlusion of the fenestration. The patient underwent emergency re-catheterization and stenting of the fenestration resulting in improved hemodynamics.

DISCUSSION

PH often develops in CHD as a result of prolonged left-to-right shunting and may ultimately be associated with a fixed increase in PVR, which may render some patients inoperable.³ The risk of developing Eisenmenger's syndrome is



Figure 3: Pre- and post-deployment changes in the mean pulmonary artery pressure in individual patients with ASDAPH.

50% in patients with a large ventricular septal defect, 90% in unrepaired atrioventricular septal defect, and almost 100% in truncus arteriosus. The timing and severity of the development of PH in CHD is directly related to the size and severity of the defect and is influenced by both the pressure and volume overload in the pulmonary arteries.³ However, the pathogenesis of PH with volume overload in ASD is not well explained by this mechanism in all the cases. Although, chronic volume overload in large or moderate-sized ASD is thought to cause irreversible changes to the pulmonary vasculature, most patients with only chronic volume overload do not develop PH. It has also been observed that in some patients with ASD, the progression rate of PH is much faster, and PH develops in childhood.

In our study, we observed there was wide variability in the size of ASDs ranging from 15 to 40 mm without direct correlation between the development of PH and the size of the ASD. Also, it was noted that there was no correlation between the duration of shunting and development of PH, as 16% of patients (n=4) in our study developed PH before the age of 18 years (Figure 3). This suggests a multifactorial cause or etiology for the development of PH in some patients with ASD, with a likely role for unknown genetic factors especially with female preponderance.⁷ The treatment of ASDAPH is controversial as treatment of PH in these patients with newer disease-modifying drugs leads to lowering of PVR resulting in increased pulmonary blood flow, which itself can lead to development of fixed PVR. The complete closure of ASDs in patients with PH using transcatheter or surgical approach is debatable as there is the potential for a deterioration of the pulmonary vascular disease with an increase in PVR and secondary signs of right heart failure without the positive effect of right-toleft shunting.¹⁰

Multiple improvisations have been attempted in surgical treatment of these patients.¹¹⁻¹⁴ In 1959, Charles P. Bailey first demonstrated the use of flap valves made of a compressed ring of polyvinyl sponge for the treatment of atrial and ventricular septal shunts in patients with severe PH. Seven of the 8 patients treated using flap valve survived.¹³ Cho YH et al reported successful surgical correction of 16 patients of secundum ASD with severe PH using a fenestrated patch.¹⁴ Although the outcome of the study was satisfactory, surgical treatment has been associated with significant morbidity and mortality. There is possibility of bleeding and arrhythmia in patients with risk for development of moderate to severe PH. Patients who develop PH immediately or several months or years after ASD closure have poorer prognosis.¹²

Interventional ASD closure in patients with normal pulmonary arterial pressures or mild to moderate PH is now widely practiced and has replaced surgical ASD closure in many centers. Partial defect closure with a fenestrated device limits the left-to-right shunt in general and allows a right-to-left shunt as a decompression mechanism during episodes of transient rises of PVR while maintaining cardiac output. As such, a fenestrated ASD closure is the only available interventional treatment option in patients with ASD and moderate to severe PH. Due to unavailability of devices with fenestrations various modifications were tried in the existing devices. As reported by Kretschmar et al, two children were treated using the standard Amplatzer devices with fenestrations made using sheath dilators and balloon stretching. These fenestrations closed spontaneously 4 months after implantation.¹⁵ Skinner et al reported closure of large ASD with severe PH using an Amplatzer device with artificially created fenestration and maintaining the patency of the created defect using a 5 mm bare metal coronary stent. In this case the patency was maintained for 39 months after the procedure.¹⁶ Creating handmade fenestrations can be risky: large fenestrations can lead to excessive shunting, desaturation, and death whereas small-sized fenestrations are at risk for spontaneous occlusion. The difficulties in creating and maintaining a fixed size, stable fenestration in the devices for ASD closure in ASDAPH led to development of the FASD device.^{17,18} Successful use of FASD device in children with ASDAPH has previously been reported by Gonzalez-Barlatay et al.19

The implantation of the FASD device is technically identical to standard ASD closure devices.²⁰ In our study, FASD implantation in all 25 patients was performed successfully at first attempt without any deployment-related complications. TTE demonstrated fenestration patency in all patients on post-implantation day 1. During follow-up, patients did not have any major complications like cardiac perforation, pericardial effusion, infective endocarditis, device erosion, embolization, and thrombus formation. No center reported any occurrence of new arrhythmias or deaths after device implantation. Spontaneous closure can occur in any fenestrated device; however, the frequency of fenestration occlusion was lower with the FASD device when compared to devices with handmade fenestrations. The occlusion of fenestration observed in one of our patients was after 6 months of implantation, which is a longer period of time than that reported with handmade fenestrations.

Symptomatic improvement was noted in most patients with improvement in NYHA functional class and improved quality of life. The symptomatic improvement may be explained by decreased left-to-right shunting, which results in normalization of RA size and pressure. The decreased RA size and pressure in the post-procedural period may help in reducing the precipitating factors for arrhythmia and make refractory arrhythmias amenable to medical treatment as was observed in one of our patients with atrial fibrillation. The decreased right-sided pressures can lead to RV remodeling, which results in improved hemodynamics. Moreover, the presence of the patent fenestration acts as a popoff valve and allows for shunting of blood from right to left in case of rise in PVR in the immediate post-deployment period and helps maintain cardiac output and oxygenation.

Limitations of Study

The retrospective nature of the study, lack of comparison to a standard treat-

ment modality, follow-up protocol, and the limited number of patients were major limitations of our study. The variation in the techniques and protocols for management of these patients based on the clinical expertise of the physician implanters, the facilities available at different centers, and the severity of comorbidities may have also influenced outcomes in this series.

CONCLUSION

ASD closure in patients with severe PH using the FASD device was beneficial for patients without any major device-related complications. The fenestrated device restricts left-to-right shunting but allows for decompression of the right heart during pulmonary hypertensive crisis. Meticulous care toward patient selection, adequate defect sizing, as well as device and fenestration size is required for optimal outcomes. Further prospective studies are required in a large cohort of patients to determine the timing of intervention, appropriate fenestration size, and long-term benefits of the FASD device in ASDAPH.

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Challenges in the Patient With Pulmonary Hypertension and Atrial Septal Defect: Understanding When and How to Close the Defect

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Associate Director of Pulmonary Hypertension Service Attending Physician Boston Adult Congenital Heart Service Assistant Professor of Pediatrics Boston Children's Hospital Harvard Medical School Boston, MA Atrial septal defects (ASDs) are common congenital heart defects in children and adults. Pulmonary arterial hypertension (PAH) is found in subsets of both pediatric and adult patients with atrial defects under varied clinical contexts. The pulmonary hypertension specialist is often faced with questions surrounding timing and method of defect closure, which may have significant impact on procedural and long-term morbidity and survival. This review highlights important differences in management between children and adults with ASDs associated with PAH, highlighting indications for closure, operability, types of closure, and long-term outcomes.

BACKGROUND AND BASELINE EVALUATION

Atrial septal defects (ASDs) are commonly diagnosed structural heart lesions occurring in about 2 per 1,000 live births.¹ Pulmonary arterial hypertension (PAH)—defined by mean pulmonary artery (PA) pressure $\geq 25 \text{ mm Hg}$, pulmonary capillary wedge pressure $(PCWP) \le 15 \text{ mm Hg}$, and pulmonary vascular resistance (PVR) \geq 3 Wood units (WU)—is a significant complication in adults with ASDs with reported prevalence of 8% to 10%.²⁻⁴ PAH in patients with ASD is linked to specific anatomic defects. There is a higher prevalence of PAH among patients with sinus venosus defects than secundum ASDs.³ Other risk factors for PAH in the setting of ASDs include residence at altitude,⁵ older age, female sex, larger size of defect, and presence of at least moderate tricuspid regurgitation.⁶ Patients with small hemodynamically inconsequential ASDs may have clinical presentation similar to idiopathic PAH. Significant PAH occurs less frequently in pediatric patients with ASDs (2.2%) and may be found particularly in children with underlying genetic cause of PAH.7 ASDs are additionally associated with pulmonary hypertension (PH) in

ex premature infants with bronchopulmonary dysplasia, perhaps reflecting effects of increased pulmonary blood flow on pulmonary vascular remodeling.⁸

ASDs are often repaired in order to optimize cardiovascular function. Benefits of ASD repair include decreased right ventricular volume overload, improved right ventricular function, and decreased PA pressure.⁶⁻⁹ However, closure of ASDs associated with PAH must be carefully considered to avoid both perioperative and long-term morbidity and mortality related to progression of PAH and right heart failure. In some cases preoperative assessment may calculate that no intervention with ensuing right to left shunt, Eisenmenger syndrome, and polycythemia may carry a better prognosis than potential perioperative complications, right heart failure, and progressive pulmonary vascular disease associated with high-risk ASD closure.¹⁰

Prior to consideration of closure, patients with PAH and ASDs should be evaluated, and if necessary and possible, treated for associated processes such as obstructive sleep apnea, chronic thromboembolism, and interstitial lung disease. Echocardiography should be performed to characterize the size, number of defects, and atrial septal

Key Words—atrial septal defect, cardiac index, indexed pulmonary vascular resistance, pulmonary arterial hypertension, pulmonary artery pressure, pulmonary hypertension, pulmonary vascular resistance, Qp/Qs: pulmonary to systemic flow ration

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anatomy (Figure 1).¹¹ Exercise testing, or 6-minute walk test, if feasible, should be completed to measure preoperative functional capacity and ascertain whether there is right to left shunting with exertion. Adult and pediatric



Figure 1: Echocardiographic imaging of atrial defects. (A) Secundum atrial septal defect in the centre of the fossa ovalis (*). Note the left-to-right flow imaged by colour Doppler (arrow). (B) Superior vena cava (SVC)-type sinus venosus defect located above the fossa ovalis between the SVC and the right upper pulmonary vein as it enters the left atrium (LA). RA=right atrium. RPA=right pulmonary artery. Reprinted from Geva T, Martins JD, Wald RM. Atrial septal defects. *Lancet.* 2014;383(9932):1921-1932. Copyright 2014, with permission from Elsevier.

Table 1. Recommendations for Closure of Simple Shunt Defects in Adults With PAH

Recommendation for Closure of ASD	ESC/ERS 2015 ¹³	ACC 2018 ¹⁴
YES	PVRi <4 WU m²	Systolic PA pressure <one-half systemic PVR / SVR <0.3</one-half
INDIVIDUALIZE	PVRi 4 to 8 WU m ²	Systolic PA pressure one-half to two-thirds systemic PVR / SVR 0.3 to 0.66
NO	PVRi >8 WU m ²	Systolic PAP >two-thirds systemic PVR / SVR >0.66 and Qp/Qs <1.0

patients with echocardiographic evidence of PAH considering ASD repair warrant full hemodynamic evaluation with cardiac catheterization to assess baseline physiological measurements including right atrial pressure, mean PA pressure, PVR, cardiac index (CI), and shunt determination (Qp/Qs).¹² During catheterization, patients should undergo acute vasodilator testing as recommended in guidelines with reassessment of hemodynamic parameters to determine pulmonary vasoreactivity. Also at catheterization, angiography should be considered to exclude the presence of peripheral pulmonic stenosis, aortopulmonary collateral vessels, and pulmonary venous anomalies.

ASD CLOSURE IN ADULTS WITH PAH

Indications for closure in adults with ASD and PAH in adults have been reviewed in consensus guidelines and are summarized in Table 1. The European guidelines generated by the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) state that moderate to large defects with prevalent systemic to pulmonary shunting and without cyanosis at rest are correctable when indexed PVR (PVRi) is <4 WU m² but due to operative risk should not be repaired when PVRi is >8 WU m^{2.13} Repair of ASDs with PVRi between 4-8 WU m² may be considered individually in specialized PH centers, carefully weighing risks and benefits of the procedure, particular patient characteristics, institutional expertise, and local postoperative care resources.

Additionally, recent American College of Cardiology/American Heart Association (AHA) Guidelines for the Management of Adults with Congenital Heart Disease include recommendations for ASD closure in patients with PAH.¹⁴ Indications for closure include impaired functional capacity, right atrial or right ventricular enlargement, and net left to right shunt (Qp:Qs) ratio >1.5:1 without cyanosis at rest or with exercise. Closure is recommended for adults with systolic PA pressure less than 50% of systemic pressure and PVR less than one-third systemic vascular resistance (SVR). ASD closure may be considered

for adults with net left to right shunt of 1.5:1 or greater, systolic PA pressure 50% or more of systemic arterial pressure, and/or PVR greater than one-third of the systemic resistance. However, these guidelines caution that ASD closure should not be performed in adults with systolic PA pressure greater than two-thirds systemic, PVR greater than two-thirds systemic, and/or a net right to left shunt.¹⁴

ASD CLOSURE IN CHILDREN WITH PAH

In pediatric patients with PH and shunt lesions, younger age at repair is an important predictor of operative survival and freedom from long-term PAH.¹⁵ A modified algorithm from the AHA/ American Thoracic Society (ATS) pediatric PH guidelines¹⁶ provides guidance for operability (Figure 2). Young patients (<1 to 2 years) with pulmonary over circulation, failure to thrive, oxygen saturation >95%, and only systemic to pulmonary shunting should undergo repair without necessarily requiring invasive preoperative catheterization. Older patients (>1 to 2 years) or those with bidirectional shunts should, how-



Figure 2: Algorithm for Management of Simple Shunts (ASD) in Pediatric Patients With PH. Reprinted from Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation*. 2015;132(21):2037-2099.

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ever, undergo hemodynamic assessment through cardiac catheterization. ASD repair is recommended for patients with PVRi <6 WU m² and PVR/SVR <0.3. For patients with PVRi >6 WU m² and PVR/SVR >0.3, acute vasodilator testing is indicated. Those with positive acute vasodilator testing response showing reversibility of PAH may undergo repair with careful postoperative PH management and consideration of closure with atrial fenestration. Repair is contraindicated for children with PVRi $>6WU m^2$ and PVR/SVR >0.3 who do not respond to acute vasodilator testing because of unacceptable operative risk related to their severe PH. These patients may, however, be considered for a treat-and-repair strategy with targeted PH therapy for a period of time followed by repeat catheterization to assess operability.¹⁷ Treated patients who subsequently show improved PVRi and positive acute vasodilator testing are considered high-risk for ASD closure, but may undergo repair with consideration of fenestration. Patients who have not improved after a period of targeted PH therapy and remain unresponsive to acute vasodilator therapy are likely inoperable with unacceptable risks of closure.

Important differences between current adult and pediatric guidelines include the use of acute vasodilator therapy to determine operability in children, as well as the potential deployment of a treatand-repair approach in pediatric patients who were previously deemed inoperable. This strategy creates the possibility for repair in patients with significantly unfavorable initial hemodynamics who demonstrate improvement and/ or response to acute vasodilator testing after a course of targeted PH therapy. It must be acknowledged that additional data are needed in support of this approach,^{18,19} and optimal vasodilator strategy and timing of therapy are yet to be determined. High-risk patients embarking on a "treat-and-repair" approach need careful postoperative follow-up to evaluate mid- and long-term results.

DEFECT CLOSURE

The mode of ASD closure, a critical choice between surgery and transcatheter approaches for PH patients with

ASDs, is no less important than the decision on whether to repair the defect at all. Transcatheter closure avoids cardiopulmonary bypass as well as surgical postoperative complications. With regard to candidacy for either approach, attention to type of defect is important as anatomy precludes transcatheter closure of ostium primum, sinus venosus, or coronary sinus defects. The size of the defects must be carefully measured. Transcatheter closure may be successfully performed for balloon stretched secundum defects <35 mm when sufficient rims of atrial tissue are available.²⁰ Additional contraindications to a transcatheter approach may include small patient size, vascular access, infectious issues, or contraindications for antiplatelet therapy post-catheterization.

Patients with ASD and elevated PVR may benefit from fenestrated ASD closure in order to preserve a residual shunt for decompression of the right ventricle and to maintain cardiac output in the event of acute rise in PVR postoperatively.²¹ This strategy may be particularly advantageous for patients with preoperative right ventricular dysfunction. The use of a fenestrated patch during surgical ASD repair has been demonstrated to be feasible in patients with severe PAH.²² Several studies have explored the use of fenestrated, commercially available transcatheter devices.^{23,24} Recently, a novel fenestrated transcatheter device, the Occlutech® Fenestrated ASD device, showed promise in a multicenter compassionate use trial of ASD closure in patients with PAH.²⁵ Additional studies of these devices will be required to determine optimal timing of fenestrated closure, effective size of fenestration, and long-term results.

BEYOND CLOSURE: CAN WE PREDICT LATE OUTCOMES?

The reported prevalence of PAH after ASD closure varies between 5% and 50%.²¹ Persistent PAH after ASD closure is associated with significant morbidity and mortality, making it important to identify patients at increased risk for progressive disease. Yong and colleagues studied a group of 215 consecutive adults undergoing transcatheter ASD closure.⁶ At 15 months



Figure 3: Outcomes After Transcatheter ASD Closure in Patients With PAH. Reprinted with permission from Yong G, Khairy P, De Guise P, et al. Pulmonary arterial hypertension in patients with transcatheter closure of secundum atrial septal defects: a longitudinal study. Circ Cardiovasc Interv. 2009;2(5):455-462. https://doi.org/10.1161/ CIRCINTERVENTIONS.108.826560. Reduction in PASP (A) and normalization of pressures (B) after transcatheter closure of ASD. A, Degree of reduction in PASP after transcatheter ASD closure according to whether patients had no, mild, moderate, or severe PAH at baseline. B, Proportion of patients with normalization of PASP (<40 mm Hg) after ASD closure, as stratified by the baseline degree of PAH.⁶

post procedure, patients with higher baseline PA pressures were more likely to experience decreased PA pressure after closure (Figure 3, Panel A) but also less likely to normalize PA pressure (Figure 3, Panel B). Among patients with moderate to severely increased PA pressures before closure, normalized pressures were associated with lower baseline pressures and no more than mild tricuspid regurgitation. Additional independent factors for normalization of PA pressures after closure included younger age and small ASD size. In a separate study, D'Alto and colleagues found high baseline value of PVRi >6 WU m² or PVR/SVR >0.33 to be associated with progressive PAH after shunt closure.²⁶ An association between age and higher PA pressures after ASD closure was also observed by Humberger and colleagues.²⁷ A multivariate logistic regression analysis of a case control cohort from a Dutch adult congenital heart disease registry additionally found pre-closure New York Heart Association functional class >1 strongly predictive of PH development after ASD closure.²⁸ In the future, novel biomarkers and genetic characteristics may prove useful for determining patients at risk for irreversible, progressive PAH after shunt closure.^{29,30}

The approach to ASDs in patients with PH involves careful preoperative clinical, imaging, and hemodynamic assessment. Guidelines have been developed to assess risk of closure in adults and childhood and may require individualized approach. A treat-and-repair strategy may be considered for patients with less favorable hemodynamics; additional data are needed to determine optimal therapies for such patients. Options for surgical and transcatheter closure should be carefully planned and the use of fenestrated surgical or transcatheter device closure may be beneficial for high-risk patients. Persistent PAH has been associated with preoperative variables including higher pressures, older age, and decreased functional class. Close clinical and echocardiographic follow-up of patients after ASD closure is essential. Following repair, clinicians should have a low threshold to reassess hemodynamics at cardiac catheterization and initiate or augment targeted PAH therapy.

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Pulmonary Vascular Disease in the Single-Ventricle Patient: Is it Really Pulmonary Hypertension and if So, How and When Should We Treat it?

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Jeffrey A. Feinstein, MD, MPH Stanford University Department of Pediatrics (Cardiology) Palo Alto, CA Despite significant improvements in the surgical and postoperative care for patients with single-ventricle physiology culminating in the Fontan circulation, significant late morbidity and mortality remains. In the setting of passive (ie, non-"pump" driven) pulmonary blood flow, pulmonary vascular resistance (PVR) plays a key role in determining cardiac output, and even slight elevations in PVR may result in significant morbidity. There is now great interest to treat Fontan patients with pulmonary vasodilators in an attempt to "optimize" PVR (and by extension, quality of life) and/ or improve an elevated PVR. This review discusses the hemodynamic implications of the Fontan circulation, the evidence for use of pulmonary vasodilator therapy, and possible target physiologic mechanisms.

The "single-ventricle" population represents a spectrum of congenital heart defects (eg, hypoplastic left heart syndrome or tricuspid atresia) where only one ventricular chamber is developed adequately enough to support systemic cardiac output. Principles in surgical management include early palliation to provide adequate pulmonary blood flow while "protecting" the pulmonary vascular bed from prolonged elevated pressures and the associated development of pulmonary vascular disease while maintaining systemic outflow. This is followed subsequently by separation of the pulmonary and systemic circulations to function in parallel, with the single pump delivering systemic output and the passive flow system delivering pulmonary blood flow. The first step is accomplished using a controlled shunt/conduit or a pulmonary artery band. Additional portions of the first operation may address structural or hemodynamic issues related to systemic cardiac output. The latter stages are accomplished with the Glenn and Fontan operations, which sequentially separate the upper body venous return from the superior vena cava (SVC) and then lower body venous return from the inferior

vena cava (IVC) by anastomosing the systemic veins directly to the pulmonary arteries.^{1,2} Both the Glenn and Fontan operations lead to a passive flow system where systemic venous return and pulmonary blood flow are dependent on low pulmonary vascular resistance (PVR) for adequate ventricular preload (Figure 1).

Over time, the surgical results and overall survival for single-ventricle palliation to a Fontan circulation have improved dramatically.³⁻⁵ Despite improved early mortality, however, significant late attrition remains. This can be attributed to a number of causes including primary cardiac dysfunction, arrhythmias, and comorbidities unique to the single-ventricle population such as protein losing enteropathy (PLE), plastic bronchitis (PB), and thromboembolic complications. With only 47% freedom from composite morbidity at 20 years, much work remains to improve quality and longevity of life in these patients.⁶ Given the reliance on low PVR for the "system" to run smoothly, there is much interest in whether FDA-approved pulmonary vasodilator therapy could improve single-ventricle circulation.7

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Fontan Procedure

Figure 1: Fontan Circulation. Passive flow of systemic venous return directly to the pulmonary arteries. RA: right atrium, PA: pulmonary artery, Ao: aorta. May LE. *Pediatric Heart Surgery: A Ready Reference for Professionals*. Fifth Edition. maxiSHARE; 2012.

Key Words—endothelial function, Fontan circulation, pulmonary blood flow, pulmonary vasodilator therapy, single-ventricle physiology

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Table 1. 10 Commandments

Age >4 years
Sinus rhythm
Normal systemic venous return
Normal right atrial volume
Mean pulmonary artery pressure <15 mm Hg
Pulmonary arteriolar resistance <4 Wood units/m ²
Pulmonary artery-aorta ratio >0.75
Left-ventricular ejection fraction >0.60
Competent mitral valve
Absence of pulmonary artery distortion

SINGLE-VENTRICLE HEMODYNAMICS

In 1977, Choussat et al. delineated 10 selection criteria for a successful Fontan operation, which are casually deemed the Ten Commandments (Table 1).⁸ Although surgical and medical techniques have improved our ability to manage deviations from several desired anatomic and functional criteria, the concept of low PVR (anecdotal evidence now suggests <2 Wood units (WU)*m² may provide the best outcomes) and low mean pulmonary artery pressure (<15 mm Hg) still hold.

Specifically, as passive flow (ie, without a subpulmonic ventricle) is dependent on a low transpulmonary gradient, even modest elevations in PVR can greatly limit pulmonary blood flow. These elevations both increase the Fontan pressure (the central venous pressure to the body) and decrease cardiac output (through decreased preload to the ventricle). This combination may result in low cardiac output from ineffective Fontan circulation even in the absence of systolic or diastolic ventricular dysfunction, rendering typical treatment strategies for low cardiac output ineffective.

Determining the optimal PVR and transpulmonary gradient in a Fontan circulation remains elusive and accurate calculation of PVR may be difficult. Furthermore, additional sources of pulmonary blood flow from a native outflow tract and/or aortopulmonary collaterals that develop over time contribute to the inaccuracies in measuring/ calculating pulmonary blood flow. Regardless, the original commandment using a PVRI cutoff of 4 WU*m² is likely too high, with most providers accepting that a normal PVR <3 WU*m² or even lower at <2 WU*m² is likely to portend more favorable long-term outcomes and prevention of late complications.

Transpulmonary gradient may be an even better estimate of pulmonary vascular health, though again differences in pulmonary artery pressure as well as interpretation of postcapillary pressure (pulmonary capillary wedge pressure vs direct atrial pressure vs ventricular end diastolic pressure) may provide different values.⁹ Anecdotally, it appears that a transpulmonary gradient >5 mm Hg is likely abnormal in this circulation.

Cardiac catheterization remains the gold standard for evaluation of Fontan hemodynamics, and cardiac magnetic resonance imaging (CMR) now adds additional flow data that may help with calculation of pulmonary blood flow and therefore PVR. Currently, there is no standard way to assess the response to pulmonary vasodilator therapy in Fontan patients similar to vasoreactivity testing performed in patients with pulmonary arterial hypertension (PAH). Anecdotally, some centers may perform testing with nitric oxide in Fontan patients to assess for a change in transpulmonary gradient or PVR, without accepted criteria for a "responder" and no data to support treatment with pulmonary vasodilators based on a response.

This is certainly an area of interest where research could identify patients who have a positive response of some sort in the catheterization lab who may benefit from more aggressive medical treatment with pulmonary vasodilators, starting with a standard way to measure hemodynamics and administer vasodilator testing. Using the standard definition of pulmonary hypertension (PH) (mean pulmonary artery pressure $\geq 25 \text{ mm Hg}$) cannot be applied to single-ventricle patients as it is uncommon to have a pulmonary artery pressure over 15 or 20 mm Hg in a patient who is tolerating the Glenn or Fontan circulation. There is a lower pulmonary artery pressure (and PVR) threshold for consideration of treatment when compared to patients

with PH. Finally, the definition of vasoreactivity for PH patients based on the adult or pediatric criteria will likely never apply to single-ventricle patients.^{10,11}

EVIDENCE FOR PULMONARY VASODILATOR THERAPY

Given the considerable interest in improving long-term outcomes for Fontan patients and the recognition that exercise tolerance even in "asymptomatic" patients is not the same as their age-matched peers, there have been several randomized studies comparing the effects of pulmonary vasodilator therapy on exercise performance in Fontan patients. In one study, the impact of sildenafil on exercise capacity in Fontan patients was assessed by exercise stress test in a randomized, crossover trial after 6 weeks of placebo or sildenafil. The group receiving sildenafil had a significant decrease in respiratory rate and minute ventilation at peak exercise. Although not significant, there was a suggestion of improvement in peak oxygen consumption at the anaerobic threshold and brain natriuretic peptide \geq 100 pg/mL in patients with single left or mixed ventricular morphology.12

Similarly, a placebo-controlled trial investigating the effect of bosentan on exercise capacity in Fontan patients demonstrated a significant increase in peak oxygen consumption (by 2 mL/ kg/min) after 14 weeks of treatment. Importantly, the side effects were not different between groups and there were no patients with hepatotoxicity, an important consideration when choosing pulmonary vasodilator therapy in Fontan patients given the population's known risk for hepatic dysfunction.¹³

An additional randomized crossover trial was performed comparing cardiopulmonary exercise test performance following a single dose of iloprost or placebo showed a significant increase in oxygen consumption following iloprost. Interestingly, the patients with low peak oxygen consumption at baseline (<30 mL/kg/min) all had higher oxygen consumption following iloprost compared to only 50% of those who at baseline had higher peak oxygen consumption. Despite only studying a single dose, this suggests that there may be a potentially beneficial effect in those with impaired exercise capacity at baseline.¹⁴

Finally, the Pediatric Heart Network is conducting a phase 3 study of the efficacy and safety of udenafil in Fontan patients 12 to 18 years of age. This randomized, placebo-controlled trial aims to assess the change in exercise capacity after 6 months of treatment with udenafil. The study does exclude those with heart failure or Fontan-related complications such as PLE and PB but may help answer the question of the utility of phosphodiesterase-5 inhibitors in asymptomatic Fontan patients.¹⁵

FAILING FONTAN POPULATION

Even more concerning than the patients who are otherwise well but at risk for long-term complications solely related to Fontan physiology are those with poor New York Heart Association (NYHA) functional class and overt symptoms of Fontan "failure." Fontan failure may refer to systolic or diastolic ventricular failure where low cardiac output is a result of pump failure, or elevated Fontan pressures as a result of elevated ventricular end diastolic pressure with a low transpulmonary gradient. It could also take the form of PLE or PB, which represent abnormal lymphatic drainage. Patients with PLE lose albumin, immunoglobulins, and clotting factors, resulting in significant fluid overload secondary to low oncotic pressure, and an increased risk for infection and thrombosis. Patients with PB develop deposits within the airways referred to as casts, which can lead to airway obstruction and respiratory compromise.

In some patients with PLE and PB, high venous pressures directly contribute to failure of normal lymphatic drainage. The thoracic duct is unable to drain normally to the venous system, and the lymphatic flow is redirected to the abdomen and thorax. Those patients may be a target for pulmonary vasodilator therapy to reduce Fontan pressure and allow improved lymphatic flow through normal channels. It remains unclear exactly what level of Fontan pressure elevation results in PLE or PB, especially as patients with expected "normal" Fontan pressures can develop these complications.

Even in the absence of typical post-Fontan complications, patients may experience Fontan failure related to elevated transpulmonary gradient alone that limits cardiac output and the ability to exercise. Typical hemodynamics in these patients would show low atrial filling pressures/ventricular end diastolic pressures and elevated Fontan pressure. As there is no way to convert the Fontan circuit to a pump to overcome this resistance in the lungs, pulmonary vasodilator therapy is particularly intriguing in this group.

Several small cohort studies have reported the effects of treatment on these Fontan patients with oral pulmonary vasodilators. Sildenafil was shown to improve PLE and PB in one study of 13 patients and to improve oxygen saturation, pulmonary artery pressure, and PVR in another of 6 patients.^{16,17} Another study showed no effect on oxygen saturation, 6-minute walk test distance, or quality of life in 10 patients treated with bosentan for 16 weeks.¹⁸ On the contrary, 8 children and 8 adolescents with $PVRI \ge 2 WU^*m^2$ treated with bosentan had reduction of PVRI after 6 months of treatment.¹⁹ Finally, a study of 6 Glenn and 12 Fontan patients showed improvement in pulmonary compliance and Nakata index of pulmonary artery size after treatment with sildenafil (n=1), bosentan (n=16), or ambrisentan $(n=1)^{20}$

As illustrated, much of the literature has focused on the Fontan population because earlier failure of single-ventricle palliation either after neonatal palliation (depending on the anatomy and amount of pulmonary blood flow after birth) or Glenn operation is more commonly related to ventricular dysfunction or other inherent patient risk factors. In addition, early attrition from the single-ventricle pathway related to pulmonary vascular disease may be better treated with heart transplantation as PVR in this group is rarely high enough to preclude transplantation and long-term outcomes in high-risk single-ventricle patients remain poor.

We retrospectively examined a group of single-ventricle patients treated with

subcutaneous treprostinil who were otherwise being considered for heart transplantation based on failing single-ventricle hemodynamics. Eighteen patients in the initial cohort received treprostinil (6 stage 1, 6 Glenn, 6 Fontan) with significant improvement in oxygen saturation and PVR in each group. In addition, 50% of patients initially ineligible for next-stage palliation were able to undergo stage 2 or 3 palliation after treatment with treprostinil and another 4 patients underwent transplantation.²¹

Along those lines, there is likely a group of high-risk patients ineligible for continued staged palliation with elevated PVR that may benefit from pulmonary vasodilator therapy. Even if heart transplantation remains the best long-term option, pulmonary vasodilator therapy may be able to reduce cyanosis and improve exercise tolerance and functional class prior to transplantation.

PATHOPHYSIOLOGY OF FONTAN CIRCULATION

Pulmonary vasodilator therapy promotes vascular smooth muscle relaxation by increasing the effect of endothelium-derived vasodilators (phosphodiesterase-5 inhibitors, prostacyclin analogues) or decreasing the effect of vasoconstrictor factor (endothelin receptor antagonists). In PAH this results in a reduction in PVR, which has been shown to improve exercise capacity in adults with an improvement in mortality over time in pediatric patients since the approval of pulmonary vasodilator therapy.¹¹

Providing nonpulsatile pulmonary blood flow, the Fontan circulation may result in alteration of pulmonary endothelial function and loss of the normal vasorelaxation response.22 One study examined lung biopsies at the time of the Fontan, grouped based on whether the Fontan was successful. In patients whose Fontan failed, there was significantly increased wall thickness of the distal pulmonary arteries and an overexpression of nitric oxide synthase.²³ Another study of autopsy specimens from 10 Fontan patients showed increased expression of endothelin-1 and endothelin receptors in the pulmonary arteries of failed Fontan patients compared to nonfailed and controls.²⁴ In addition, there

was significant medial hypertrophy with intimal thickening in the failed Fontan group with significant lower expression of endothelial bone morphogenetic protein receptor type 2 (BMPR2).²⁵ Determining the alteration in endothelial function and balance of vasodilatory factors specific to the Fontan operation would be essential to tailoring PAH therapy to this population.

There are also data that suggest longterm pulmonary vascular remodeling in the Fontan circulation may be quite different than in PAH. In a series of 12 Fontan patients who died either early after the Fontan operation (n=5) or >5years following the Fontan (n=7), analysis of intra-acinar pulmonary vessels from lung tissue obtained at autopsy showed decreased medial thickness with a reduction in vascular smooth muscle, which was proportional to the length of time since the Fontan operation.²⁶ This suggests approved PAH therapy may not have the same effect in the long-standing Fontan circulation. However, even late after the Fontan operation, the pulmonary vasculature has been shown to be reactive to nitric oxide with a reduction in PVR, suggesting there may be a response to pulmonary vasodilator therapy and stressing the importance of developing a protocol for a form of vasoreactivity testing to determine which patients may benefit from therapy.²⁷

CONCLUSION

Experts recently published a letter to the editor following a meta-analysis that concluded that pulmonary vasodilator therapy improves exercise capacity, hemodynamics, and functional class in Fontan patients.²⁸ The letter, entitled "Pulmonary vasodilator therapy as treatment for patients with a Fontan circulation: the Emperor's new clothes?" raises concerns about the heterogeneity of the populations previously studied, limited knowledge about pulmonary vascular remodeling in the Fontan circulation, and current lack of randomized controlled trials, especially late after the Fontan operation involving more than a single dose of therapy.²⁹

Overall, there are several promising studies, particularly in subgroups of symptomatic patients, that suggest some patients with Fontan circulation may benefit from pulmonary vasodilator therapy. At this time, however, there is no evidence to routinely recommend pulmonary vasodilator therapy for all Fontan patients. We have yet to determine who would benefit from long-term therapy and research should continue to focus on understanding the hemodynamic and clinical effects of pulmonary vasodilator therapy in Fontan patients as well as identifying which patients would benefit most from therapy.

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Pressure vs Flow-Induced Pulmonary Hypertension

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The pathophysiology of pulmonary hypertension (PH) is multifactorial, complex, and incompletely understood.^{1,2} However, it is known that abnormal mechanical forces within the pulmonary vasculature participate in the disease process.³ The pulmonary vasculature is continually exposed to hemodynamic forces that include: (1) shear stress, the tangential friction force acting on the vessel wall due to blood flow^{4,5}; (2) hydrostatic pressure, the perpendicular force acting on the vascular wall⁶; and (3) cyclic strain, the circumferential stretch of the vessel wall.^{7,8} Mechanosensors on pulmonary vascular endothelial cells detect these forces and transduce them into biochemical signals that trigger vascular responses (Figure 1).9,10 Among the various force-induced signaling molecules, nitric oxide (NO), reactive oxygen species (ROS), and endothelin-1 (ET-1) have been implicated in vascular health and disease.¹¹⁻¹² For example, increases in physiologic shear stress associated with increased cardiac output (ie, during exercise) result in induction of NO production with decreased ROS and ET-1, facilitating pulmonary vasodilation and increased flow. However, the pathologic pulmonary vasculature may induce supraphysiologic levels of shear stress, pressure, and cyclic strain resulting in decreased NO with increased ROS and ET-1.13,14 Thus, abnormal hemodynamic forces develop in and participate

in the disease progression of most forms of pulmonary vascular disease (PVD).¹⁵ However, the influence of hemodynamic forces in the pathobiology of PVD is most clearly demonstrated in patients with PH secondary to congenital heart disease (CHD).¹⁶

PH SECONDARY TO CHD

CHD remains one of the most common worldwide causes of PVD,¹⁷ and represents 45% to 55% of all pediatric PVD.¹⁸ In these patients, structural cardiac abnormalities result in increased flow within the pulmonary vasculature with or without a direct pressure stimulus from the systemic ventricle—that in turn cause well-described progressive histopathologic changes within the pulmonary circulation.^{19,20}

Classification of PVD associated with CHD belies the complexity and varying physiology of predisposing cardiac lesions-from the classic example of unrestrictive ventricular septal defect (VSD) to complex single-ventricle lesions. The natural history of PVD associated with systemic-to-pulmonary shunt reveals the differential, or perhaps incremental, effects of increased pulmonary blood flow and increased pulmonary arterial pressure. In patients with increased blood flow alone-pre-tricuspid valve lesions such as atrial septal defects (ASDs)-the development of PVD is uncommon and presents late,

among 5% to 15% of patients by the fourth decade of life.²¹ In stark contrast, in patients with increased blood flow and a direct pressure stimulus from the systemic ventricle—post-tricuspid lesions such as unrestrictive VSDs or truncus arteriosus-the development of PVD is common, and develops early in life. The progression of PVD in these lesions reflects the differing hemodynamic insults to the pulmonary vasculature. In addition, genetic predispositions and/or differences in oxygen tension delivered to the pulmonary vasculature likely participate in disease progression, and represent an important, yet poorly understood area of investigation.^{1,22,23} A summary of the risk of developing



Figure 1: Biomechanical Forces Regulate Vessel Tone. Vascular tone is regulated by the opposing effects of vasodilators and vasoconstrictors that are predominantly produced by the vascular endothelium. These bioactive factors are heavily regulated by biomechanical forces such that laminar SS (LSS) stimulates factors that enhance vasodilation while cyclic stretch (CS) enhances vasoconstriction.

Key Words—congenital heart disease, cyclic strain, hydrostatic pressure, pulmonary vascular disease, shear stress

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Table 1. Risk of PVD in Differing Lesions Associated With CHD and Increased Pulmonary

 Blood Flow.²⁴⁻²⁷ These data are adapted from reference 98.

CHD WITH INCREASED PULMONARY BLOOD FLOW AND/OR PRESSURE						
DEFECT	AGE OF OCCURRENCE					
Truncus Arteriosus	~100%	<2 years				
A-V Septal Defect	~100%	~2 years				
Transportation of Great Arteries + VSD	~70%-100%	1-2 years				
Patent Ductus Arteriosus	~15%-20%	>2 years				
Ventricular Septal Defect	~15%-20%	>2 years				
Atrial Septal Defect	~20%	>20 years				

Defects in bold and italics represent high-flow/direct high-pressure lesions; defects in italics represent high-flow/variable direct high-pressure lesions; ASD is a high-flow lesion without a direct pressure stimulus from the systemic ventricle.

irreversible PVD with different lesions associated with increased pulmonary blood flow and the age of development is described in Table 1.

Thus, the investigation of the effect of specific physiologic and pathophysiologic hemodynamic forces on the pulmonary vasculature may lead to targeted therapeutic approaches for PVD secondary to CHD, as well as inform other types of PVD, in which abnormal mechanical forces participate in disease progression. Using endothelial cell monolayers, a growing body of *in vitro* literature informs the effect of different types and magnitudes of biomechanical forces on endothelial cell function. These data are summarized in the following two paragraphs.

REGULATION OF ENDOTHELIAL VASOACTIVE FACTORS BY BIOMECHANICAL FORCES: IN VITRO STUDIES Vasodilators: NO, Prostacyclin,

Endothelium-derived Hyperpolarizing Factor

Nitric oxide is a vasorelaxant produced by NO synthase isoforms converting L-arginine to citrulline. In the blood vessels, NO is synthesized in the endothelial cells (ECs) and diffuses to the adjacent smooth muscle cells (SMCs), where it activates soluble guanylate cyclases (sGC).²⁸ This leads to activation of cGMP-dependent PKG and other effector proteins, including ion channels, ion pumps, and phosphodiesterases (PDEs).²⁹ NO is also known to inhibit platelet aggregation and inhibit SMC proliferation. Physiologic laminar shear stress (SS) is well known to increase NO production via endothelial NO synthase (eNOS) phosphorylation and/or stimulating EC receptors and increasing intracellular Ca²⁺.³⁰ Exposing ECs to laminar SS can also suppress ROS levels.³¹⁻³² Importantly, exposing ECs to either pathologic low or high levels of laminar SS, or irregular flow patterns, leads to higher levels of ROS and less available NO.³³⁻³⁴ A large body of evidence demonstrates that patients with advanced pulmonary vascular disease have decreased bioavailable NO and increased ROS production.³⁵ Importantly, patients with PVD secondary to CHD also demonstrate early aberrations in NO production.36

Derived from arachidonic acid within the EC, prostacyclin (PGI₂) is another vasodilator with a broad range of effects on the vasculature that is induced by flow (laminar SS). Prostacyclin binds to the prostacyclin receptors (IP),³⁷ which are located on both platelets and SMCs³⁸ and that leads to inhibition of platelet aggregation.³⁹ Acting via G GPCR prostaglandin receptors, it induces cAMP synthesis and well-described PKA-dependent pathway of the cytoskeletal reorganization and relaxation.⁴⁰ The effects of PGI₂ are tightly related to NO effects since PGI, potentiates NO release and, in turn, NO potentiates the effect of PGI, on SMCs.⁴¹ Prostacyclin possesses antiproliferative activity toward SMC and has anti-inflammatory effect inhibiting proinflammatory cytokines and activating anti-inflammatory cytokines expression. PGI, also exerts protective effects in the vasculature

by inhibiting SMC hypertrophy, migration, and proliferation.⁴² Decreased PGI₂ has been demonstrated in the lungs of patients with advanced PVD.⁴³ *In vitro* studies demonstrate increased PGI₂ secretion during physiologic shear stress, but decreased release during pathologic levels of shear and cyclic stretch.⁴⁴

Endothelium-derived hyperpolarizing factor (EDHF) produced by the EC is a vasodilator of unknown nature, which has been shown to be important for vascular tone in smaller arteries.⁴⁵ Vasorelaxation occurs following endothelial stimulation through a non-NO, non-prostanoid pathway originally ascribed to the actions of EDHF.⁴⁶ EDHF involves hyperpolarization, generated in the endothelium, which spreads via myoendothelial gap junctions to the SMCs, and it is this hyperpolarization that results in relaxation of the vascular SMCs.⁴⁷⁻⁵⁰ Flow-induced vasodilation that is independent of endothelium-derived NO and PGI, is typically due to EDHF.⁵¹ EDHF initiates SMC hyperpolarization directly following its release from the endothelium.⁵²⁻⁵³ The endothelial hyperpolarization is initiated by the activation of KCa channels.⁵⁴ H_2O_2 is believed to be an EDHF that acts primarily on the prearterioles and arterioles where EDH-mediated relaxation becomes more important than EDNO.⁵⁵⁻⁵⁷ Shear stress can induce the release of H₂O₂ from ECs, which acts as an EDHF that contributes to flow-induced vasodilation in coronary arterioles.⁵⁸ H₂O₂ can induce this hyperpolarization by several mechanisms including cGMP or cAMP-meditated pathway, activation of PKA/PLA2, or the direct activation of various K+ channels.⁵⁹

Vasoconstrictors: ET-1, Thromboxane, Angiotensin II

Endothelin-1 is a 21 amino acid polypeptide produced by the EC that induces potent vasoconstriction and SMC proliferation. ET-1 is a GPCR agonist inducing Ca^{2+} elevation in affected cells. In the vasculature, ET-1 has pleiotropic effects producing SMC constriction via ET_A receptors and inducing relaxation via endothelial ET_B receptors.⁶⁰ Increased ROS production caused by ET-1 promotes vasoconstriction and vascular remodeling, in part, via the suppression of NO activity.⁶¹ However, physiological levels of shear stress have a negative effect on the expression of ppET-1 and ET-1-converting enzyme (ECE-1) in the EC.65-66 This downregulation of the ET-1 system depends on eNOS activation and oxidative stress.⁶⁶⁻⁶⁷ Conversely, cyclic stretch significantly upregulates preprET-1 mRNA expression in ECs.⁶⁸ A wealth of evidence implicates ET-1 signaling in the pathophysiology of PVD secondary to CHD. For example, ET-1 mRNA and peptide expression are significantly upregulated in PH models and patients,⁶²⁻⁶⁴ and ET-1 levels are increased in both the plasma and lung of patients with PVD and, importantly, correlate with disease prognosis.62,63,69

Another arachidonic acid derivative, Thromboxane A_2 (Tx A_2), is secreted by platelets, inducing platelet aggregation, thrombosis, and reducing blood flow. TxA₂ promotes platelet aggregation and expresses adhesive cofactors for platelets such as von Willebrand factor, fibronectin and thrombospondin, and procoagulant factors.⁷⁰ TxA, exerts its biological activity through its cognate TP GPCR receptor.⁷¹ TxA₂ receptor is known to promote cell migration and proliferation of SMCs.72-74 Thromboxane is a functional antagonist of prostacyclin and balance between them supports vascular homeostasis. Interestingly, in vitro studies demonstrate decreased TxA₂ secretion during physiologic SS, but increased release during pathologic levels of shear and cyclic stretch.75,76

Angiotensin II (Ang II) is produced from angiotensin I in the lung tissue by angiotensin-converting enzyme (ACE). Ang II is a potent vasoconstrictor acting via GPCR Ang II type 1 and type 2 receptors (AT1R and AT2R). Activated G_a GPCR AT1R stimulates phospholipase C pathway and increases intracellular Ca²⁺ levels via IP₃ receptors. Ang II promotes SMC remodeling, cell growth, fibrosis, collagen deposition, and contractility.⁷⁷ Shear stress can upregulate ACE expression in SMCs.⁷⁸ AT1R is also likely a redox-coupled mechanosensor that regulates oxidative stress, as studies have demonstrated that AT1R is closely associated with ROS production.⁷⁹⁻⁸¹ Interestingly, laminar SS can induce ROS by AT1R-mediated downregulation of eNOS expression, which is dependent on Akt and Erk activity.⁸²

Although these *in vitro* studies have been very informative, several limitations are noteworthy. For example, traditional studies of EC mechanotransduction are performed utilizing EC monolayers.83 Therefore, important interactions between ECs and SMCs are not captured during these studies. In addition, replicating in vivo forces in in vitro cell culture experiments is fraught with difficulties, including the estimation of the magnitude, type, and duration of the mechanical perturbations, as well as the inability to apply simultaneous differential forces as occur in vivo.84-87 For example, the amount of cyclic stretch that results from a particular force will also be dependent on the compliance of the blood vessel. In addition, EC mechanotransduction is dependent on the developmental stage and vascular bed of the EC investigated. Therefore *in vitro* studies must be correlated with observations made *in vivo* in clinically relevant models of human CHD.

PRESSURE VS FLOW: IN VIVO STUDIES

Animal Models

To understand the impact of increased pressure, flow, or both on the pulmonary

vasculature, animal models of CHD provide insight on the progression and mechanisms of PVD and allow for preclinical testing of pharmacologic or other interventions.⁸⁸ Low pulmonary blood flow, high pulmonary arterial pressure and resistance, and a dominant right ventricle characterize normal fetal physiology.⁸⁹ At birth, dramatic changes in pulmonary blood flow (PBF) patterns occur, most notably a rise in PBF and decline in vascular resistance.90 Associated with these changes are dramatic changes in gene expression patterns, including cascades that have been implicated in the development of PVD.⁹¹ However, in the setting of CHD these birth-related changes are altered; a delayed increase in PBF after birth is well characterized.^{92,93} Therefore, in order to truly simulate CHD, fetal creation of the defects is essential. To this end, we initially created a model of increased PBF and pressure by placing a large Gore-Tex graft between the ascending aorta and pulmonary artery in late-gestation fetal lambs.⁹⁴ This model mimics lesions such as a large VSD. Not only does the physiology of this model mimic infants with common CHD, the biochemical and gene expression alterations described also mimic infants with CHD.⁹⁵ To investigate the *in vivo* effects of flow alone, we have recently developed an ovine model of increased PBF to the right lung following in utero ligation of the left pulmonary artery. Our preliminary data demonstrate the expected physiologic differences in these models (Table 2). Shunt lambs have both increased PBF and pressure, while the right lungs of LPA ligation lambs have increased PBF with a very modest increase in pressure. Importantly, the

Table 2. Baseline Hemodynamics in (control (n=9), LPA Ligation	(n=8), Shunt $(n=4)$ Lambs.
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	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR bpm	PA SBP (mmHg)	PA DBP (mmHg)	MPAP (mmHg)	∆ PAP (mmHg)	RPAQ (L/ min)
Control	97±12	57±8.6	70±9.4	118±21	20±3.4	8.5±1.6	14±1.8	11.8±0.2	0.7±0.1
LPA	106±17	58±14	74±15	121±16	27±5.2*	12±3.3*	19±3.6*	14.8±3.2	1.4±0.3*
Shunt	118±5.7*	36±8.5*	61±8.7	126±17	35±9.2* Y	18±5.1* Υ	26±6.3* Y	18.±0.4* Y	2.0±0.2* Y

P<0.05 vs control. ΥP <0.05 shunt vs LPA ligation lambs. For control and shunt lambs, right pulmonary artery pulmonary blood flow (RPAQ) was estimated assuming 55% of total PBF to the right lung. SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; HR=heart rate; PA SBP=pulmonary artery systolic blood pressure; PA DBP=pulmonary artery diastolic blood pressure; MPAP=mean pulmonary arterial pressure; Δ PAP=pulse pulmonary pressure; MPAQ=main pulmonary artery blood flow; RPAQ=right lung pulmonary artery blood flow.

pulmonary pulse pressure is only elevated in shunt lambs.

To begin to investigate the effects of pressure + flow vs flow alone on endothelial function in vivo we compared ET-1 and NO production in shunt, LPA ligation, and age-matched control lambs. Interestingly, ET-1 levels are increased in shunt lambs, but not in LPA ligation lambs. Correlative in vitro studies demonstrate that cyclic stretch applied to normal pulmonary artery endothelial cells (PAECs) increases ET-1 levels, while shear stress decreases ET-1 levels. Not surprisingly, eNOS protein expression is increased in both shunt and LPA lungs, which likely represents flow (shear stress) eNOS induction. However, NO metabolite (NOx) levels are increased in LPA lungs, but decreased in shunt lungs (data not shown). These data suggest eNOS uncoupling in shunt lambs, as we have previously described,96,97 but maintenance of eNOS coupling in LPA ligation lambs.

We next sought to examine the gene expression profile of PAECs, which are primarily affected by both shear (increased PBF) and cyclic stretch (increased pulmonary pressure.) We first performed RNA sequencing on PAECs derived from control, LPA, and shunt lambs. Principal clustering analysis (Figure 2A) demonstrated excellent differentiation between PAECs derived from each model, as did dendrogram and unsupervised hierarchical clustering heat map analysis (Figure 2B). These data provide visualization for transcriptome-level differences between models. Although important differences exist, the LPA ligation model (increased pulmonary arterial flow only) is the most similar to control, while shunt lambs (increased pulmonary arterial pressure and flow) have more differences in RNA expression, both in terms of significance and fold change.

CONCLUSION

The natural history of pulmonary vascular disease associated with CHD suggests distinct pathophysiologic consequences of different hemodynamic insults to the pulmonary vasculature. Classic *in vitro* studies demonstrate significant differences in the endothelial response to



Figure 2: Transcriptional Characterization of Control, LPA, and Shunt PAECs. N = 3 control, n = 3 LPA, n = 3 shunt. (A) Principal component analysis and (B) heat map of PAEC RNA-Seq data confirm clustering of gene expression by model. These data are adapted from reference 98.

differing types, duration, and magnitude of biomechanical forces. Our preliminary in vivo studies demonstrate substantial differences between the animals with normal physiology, those with increased pulmonary blood flow alone (LPA), and those with increased pulmonary pressure and flow (shunt) both in NO/ET-1 signaling, and in the proximal pulmonary artery endothelial cell transcriptome. Given the significant burden of PVD among patients with CHD particularly in the pediatric population, a fundamental understanding of the differing mechanisms leading to vascular pathology associated with different CHD lesions provides an essential tool in tailoring therapy to these patients. As medicine is increasingly focused on personalized and precision approaches, improved in vitro techniques, and improved animal models of CHD are needed to separate the effects of differential mechanical forces on the pulmonary vasculature. These data may yield important mechanism-specific therapeutic strategies for patients with differing CHD as well as other forms of PVD.

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The Crossover From Child to Adult With PH and Congenital Heart Disease

Guest editor Dunbar Ivy, MD, Chief of Pediatric Cardiology and Director of the Pediatric Pulmonary Hypertension Program at the University of Colorado School of Medicine and Children's Hospital of Colorado led a discussion among Editor-in-Chief Harrison (Hap) Farber, MD, then Professor of Medicine and Director of the Pulmonary Hypertension Center at Boston University/Boston Medical Center; Mary P. Mullen, MD, PhD, Assistant Professor of Pediatrics at Harvard Medical School, associate cardiologist at Boston Children's Hospital and Associate Director of the Pulmonary Hypertension Service as well as a member of the adult congenital heart program; Jeffrey R. Fineman, MD, Professor and Vice Chair of Pediatrics, Director of Pediatric Critical Care Medicine and Pulmonary Hypertension, University of California, San Francisco, Benioff Children's Hospital; and Gareth Morgan, MD, Associate Professor of Pediatrics-Cardiology at the University of Colorado School of Medicine and Director of the Cardiac Catheterization Lab at Children's Hospital of Colorado.

Dr Ivy: I am pleased to be the guest editor for this issue of Advances in Pulmonary Hypertension. This issue is dedicated to the crossover between the adult and child with pulmonary hypertension and congenital heart disease. Several important gaps are recognized between our knowledge and treatment of adults and children. These are readily apparent in the guidelines, which have been published recently by the European Respiratory Society, as well as in the journal Circulation. These are the adult guidelines for PH and the pediatric guidelines for pulmonary hypertension. In the adult guidelines, there are very strict criteria for operability. And these criteria do not allow for a so-called treat-and-repair approach, where the patient would be treated with medication and then undergo a repeat catheterization and then a reconsideration of defect closure. In contrast, in the pediatric guidelines there is a potential for a treat-and-repair strategy, whereas patients who would not be reactiveand we can discuss these criteria—could be treated and then reconsidered for surgical operability. So, I'd like to start our roundtable with Dr Mary Mullen, who can talk a little bit about these differences between children and adults.

Dr Mullen: There are clear differences between the adult and pediatric guidelines for operability in pulmonary hypertension. Regardless of patient age, predicting successful short-term and longer-term outcomes in patients with congenital heart disease is essential and really requires careful consideration of hemodynamics. We assess PVR, PVR to SVR ratio, and pulmonary-to-systemic blood flow in all patients. There are, however, differences in the guideline-based approaches between adult and pediatric populations. With regard to simple shunt lesions such as ASD, VSD, and PDA, European guidelines for adults state that patients with indexed PVR greater than 8 Wood units would not be correctable while those with indexed PVR less than 4 Wood units could undergo operation. Those with PVRI between 4 and 8 may have individual approaches. The pediatric guidelines take into consideration short-term acute vasodilator response to determine ability to proceed with operability and may include a treat-and-repair strategy. Again looking at simple shunt lesions, pediatric guidelines state that an index PVR less than 6, potentially with complementary response to acute vasodilator testing, would allow proceeding to operation. With PVRI greater than 6 you would definitely need a positive acute vasodilator response to proceed to repair. For PVRI >6 without a response to acute vasodilator testing, one should consider a treat-and-repair strategy with target pulmonary hypertension therapy, which would require repeat catheterization. At this junction those with acute vasodilator response could undergo high-risk surgery, considering fenestration while those without positive AVT are probably inoperable.

Dr Farber: So, the question I have is, because all I do is adults: it seems like we're seeing more and more patients, probably because of certain immigration patterns as well as patients diagnosed later in life, who have either an ASD or anomalous pulmonary venous drainage and have fairly significant pulmonary hypertension. Nobody really wants to operate on them because most of them have a PVR >6 or >8. And so, we're forced to treat them medically. Let's say we do have a patient who has a reasonably good response to PAH-specific meds and gets their numbers down. What a lot of people have done, at least in adults, is to look at RV cardiac index and RV end diastolic pressure combined with the PVR and see if we can make it to a manageable number that somebody thinks they could survive surgery. Does that make any sense?

Dr Ivy: I think it makes sense. We have certainly used a similar approach in some patients. We've been referred some adults that have sinus venosus atrial septal defect, partial anomalous pulmonary venous return, who have been treated with triple therapy and after several years of therapy, we can get the pulmonary vascular resistance <6 and have elected to do surgical repair with a fenestration. I think that the challenge that I don't think we know as a field is none of these are prospective studies.

Dr Farber: Oh, no, not at all.

Dr Ivy: They are all case series, or a retrospective look, saying, "Oh, we got through the surgery and this is how we did it." If you look at some of the papers from Professor Galiè and some from the pediatric literature, one of the groups with the highest risk of late mortality is those patients who have had complete repair of congenital defects with existing pulmonary vascular disease. So, I think there is a lack of knowledge, and I think in the adults maybe because of the length of time these patients have had significant pulmonary vascular disease. There's less appetite for risk. Whereas in a young child, I think we're more willing to take that on. But again

Dr Farber: There's another potential point, just listening to this: the fact that in those people that seem to have a reasonably good response to pulmonary vasodilators, maybe they'd do better if we just left them alone and treated them medically, rather than surgically. But as far as I know, there are no studies looking at that, either.

Dr Fineman: So, I don't take care of any adults, but certainly in the pediatric population, we've been pretty aggressive about this treat-and-repair approach. And perhaps, well after we're all retired, we'll know whether we're doing the right thing or not. In other words, will these patients' PVRs remain low or re-emerge with PAH? But I could tell you that certainly, particularly with some of the children with complex cyanotic lesions like TGA/VSD that we've done, there is no question they feel better and thrive. Their saturations are better. They start developing normally, etc. The big question for us is just what you brought up, Dunbar, is are they going to show up 5 or 10 years from now with advancing pulmonary vascular disease and then, clearly, they would have done better if we would have left them alone? And so, the question that we always entertain is not really should this be a treat-andrepair, but should it be treat, repair, and continue to treat? And should we treat for how long and with what?

Dr Mullen: Right. Well, I think the point you raised is a very good one.

Because clearly, we need to reassess by catheterization any patients with elevated PVR who undergo repair and certainly continue treating if there is residual elevation in PVR or elevation in mean PA pressure. Generally we would repeat catheterization 3 to 6 months post surgery. In both pediatric and adult patients we also need to assess comorbidities, including obstructive sleep apnea, co-existing lung disease, or aspiration, and continue close follow-up, so that there are no other issues that increase propensity to pulmonary vascular disease long term.

Dr Fineman: Well, the other thing is should we, particularly with the atrial septal defects, should we be doing genetic screening on them? Would that change our approach in terms of how aggressive we would be?

Dr Ivy: We saw a child who had a sibling that died from pulmonary hypertension many years ago. She had a moderate to large atrial septal defect; was incredibly reactive; had acute Qp:Qs on room air of greater than 2-1/2:1. We elected to completely repair the defect at that time and then treated her with pulmonary vasodilator medications, including intravenous epoprostenol. Ten years later, she moved back to her native country and was able to continue her therapy, but she died suddenly from a pulmonary hypertensive crisis. So, if you had a patient with familial disease, that may make me want to see a lower PVR and consider fenestration before considering correction. But again, that's a case of one. I think Dr Morgan had something to add?

Dr Morgan: I'm not a pulmonary hypertension specialist, so I've enjoyed listening to the conversation. I have just a couple of comments. I always find the "PH with ASD" conversation particularly interesting because I haven't yet really been convinced by the data that ASDs cause Eisenmenger syndrome. I'm always, therefore, interested in the interaction between the presence of an ASD and pulmonary vascular disease. But I wanted to take a step back. We talked about data available in adult practice for

degrees of vascular resistance that make complete repair appropriate. Again, you guys may be familiar with it, but there is certainly some work from the group that I used to work with at King's College in London led by Dr Kuberan Pushparajah and Dr Tarique Hussain (who is now in Dallas, Texas) looking at MRI-calculated pulmonary vascular resistance and operability, both in the single ventricle and biventricular groups. And they got some pretty convincing data that in the pediatric population procedural reversibility is not as important as the baseline vascular resistance number that is calculated. They certainly felt that for the biventricular patient that a PVR of <6 meant that patients could be pretty confidently operated upon with a complete repair.

Dr Farber: Meaning no fenestration?

Dr Morgan: Yeah, with no fenestration. And likewise for single ventricle patients, patients with functioning univentricular hearts, that they could safely complete the Fontan procedure with a PVRI of <4, irrespective of reversibility with those numbers. So, I'm not sure how much more quantitative data that there are in the pediatric world, but it is starting to creep out obviously and guiding numbers are starting to become available. I do think that a lot of our discussion about congenital patients is qualitative and based on gut feeling a little bit. And it would be nice to see a little bit more science developing this conversation to allow us both to determine when complete repair or fenestrated repair is possible. Another question that was raised during this roundtable is which patients need to continue on therapy for at least a period of time after the repair is done?

Dr Ivy: The presence of a PFO is a positive long-term predictor for patients. Julio Sandoval in Mexico City for years has done balloon atrial septostomy for patients with idiopathic pulmonary arterial hypertension, with pretty reasonable results. So, it's a very complex decision that you would think would be quite easy.

Dr Farber: It's interesting. Because in his case, he started doing them really out

of necessity, because they really had no alternative, as there weren't PAH-specific medications available in Mexico. But he has done so many that he is really good at it. And their numbers are far better and far exceed anything that any of us in the adult world have ever come close to doing. It's probably once again this issue that they've done so many; they pick the patients much better than we do; and they're just better at it.

Dr Morgan: Do you think he's better at it because he's good at determining how big a hole to make? Or is it patient selection?

Dr Farber: I'll bet it's a combination of that and likely other factors.

Dr Morgan: Yes.

Dr Ivy: It's certainly patient selection. Predictors of procedure-related death include a mean right atrial pressure >20 mm Hg, a pulmonary vascular resistance index of >55 Units, and resting saturation <90%. So, Dr Fineman, I was curious what your insights were in terms of what we really know about ASD and Eisenmenger. I hear people that are strongly on one side or the other.

Dr Fineman: I'm advocating for genetic testing on all of these isolated ASDs. I just wonder how much of a subset of them happen to be, for a better word, idiopathic, and have a coincidental ASD. You know, there's such variability in both the frequency and the age that it presents, it just makes you wonder. In some of the animal data, which I've put a little bit into the paper in this issue of Advances-and we have a much larger paper in review right now-we compare the effects of a pressure and flow stimulus on the pulmonary vasculature versus just increased flow alone. There clearly, not just from a physiologic and biochemical perspective, but from a broad transcriptional perspective, are marked different transcriptional patterns, depending on flow alone versus pressure plus flow. In other words, an ASD versus an unrestricted VSD. And the heat map, the transcriptome pattern of the flow alone, is not that dissimilar

to normal. There are some intermediate effects that make it vulnerable to a secondary insult. But there's no question that the two stimuli, pressure and flow combined versus flow alone, are very, very different on the pulmonary vasculature. And so for me, one of the arguments about treating prior to repair is that you're going to take a kid who may have a Qp:Qs of 1.2 to 1 and give him a Qp:Qs of 3 to 1 for a period of time. I'd be happy obviously if we can generate such a large Qp:Qs, because we're obviously decreasing PVR. But for that period of time, I mean, in terms of increasing pulmonary blood flow at a lower pressure for 6 months prior to surgical correction, at least from the animal data, doesn't concern me that I am causing more harm during the pre-op treatment period. Obviously, you need to treat them symptomatically. But I don't think flow alone is nearly the negative stimulus than when you put a pressure head with it. I don't know if that answered your question or not?

Dr Farber: Well, no. But in a way, that makes sense because as an adult pulmonary hypertension person, a lot of these people we see with an ASD, even a large one, don't present until they're in their 50s or 60s

Dr Fineman: Right, right, right.

Dr Farber: And they've just had increased flow their entire life and probably minimal, if any, increase in pressure.

Dr Fineman: Right, right.

Dr Morgan: Jeff, I think your commentary there is really interesting to listen to. And again, as a nonpulmonary hypertension, nonscientist, indeed from the viewpoint of a clinical plumber, I found that to be a very clear explanation that fits with my nonscientific concept of ASDs and PH; the whole idea of upregulation of all the things that are at play in patients who've got increased flow. But I do think a lot of people, in my experiences particularly in the adult pulmonary hypertension setting, a lot of clinicians find that a difficult concept and find it difficult to separate the congenital ASD patient from the patient who's had maybe a pressure-driven VSD or PDA-type shunt for a long period of time, who then has a much—in my opinion—easier to understand, vasculature change that's occurred because of a pressure head pummeling the pulmonary circulation.

Dr Fineman: Sure.

Dr Mullen: Clearly there is a different phenotype in the pediatric patient who presents with a large ASD and has elevated resistance from the very start of monitoring—this may be a completely different phenotype. I think the discussion about genetic testing is very provocative and very important, you know, because it would be helpful to understand both subgroups. I was interested in what Dunbar said about taking that into consideration in terms of repair. I think we need more follow-up information about operability of such phenotypes to discern true differences. It may be that certain groups or subsets of genetic mutations causing pulmonary hypertension may be more susceptible to flow and we would really want to make sure that we close them early. I think the data are just not there yet.

Dr Ivy: So, there's a recent paper from a consortium across the US that Wendy Chung wrote, that a gene called *SOX17*, which produces a transcription factor that's involved in embryonic development, may be an early clue as to why some people with congenital heart disease develop early pulmonary vascular disease. It will be interesting to see how things play out in the next few years, in terms of again our ability to predict who is going to do well and who won't.

Dr Farber: There's a large study of PAH patients in Britain. The government actually funded it to sequence all PAH patients. And the British now have collected about 1,000 individuals who have true PAH. And when you look at all the genetic defects they found, *SOX17* does show up every once in a while.

Dr Farber: Maybe that it is another mutation among who knows how many

mutations that we know and most that we don't know that might play a role or increase your risk for PAH or idiopathic disease.

Dr Ivy: So, I think I'd like to take the opportunity to discuss the scientific manuscript in this issue on use of the Occlutech[®] device. And I'd like for Dr Morgan just to give us a brief overview of the paper. And then maybe we can all comment on how a device like this might change our clinical practice.

Dr Morgan: Yes, thanks, Dunbar. Conceptually, I don't think there's anything new about the concept of this device. In fact, Kurt Amplatz actually developed a fenestrated device similar to this more than a decade ago, but for various market reasons, Amplatzer withdrew it from their shelves. Occlutech, who are pushing quite hard at the concept of fenestrated devices, both fenestrated ASD closure devices, but also related to this, the device that is known as the AFR, the atrial flow regulator, which is a controlled septostomy-type device, to give you a defined-sized hole in the septum. This AFT is planned to be used for patients with both pulmonary hypertension and those with left ventricular diastolic dysfunction to allow passage of flow between the atria in a controlled way. And so, as a concept, I think this whole idea is quite familiar to us all. The senior author is Joseph Vettukattil from Spectrum Health Helen DeVos Children's Hospital in Grand Rapids, Michigan. And basically, we gathered all the compassionate cases around the world for the Occlutech fenestrated ASD closure device, including some patients from the USA, but also a lot of patients in Europe and in Britain. So, it's a motley crew of patient characteristics and pathology, as it describes compassionate use cases gathered together. But from a technical point of view, it does show that the device is easily deployable and does create a reliable fenestration that stays open in at least the medium term. Therefore, it can allow potential decompression in the face of rising atrial pressures in events such as a pulmonary hypertensive crisis. Although it's not a prospective controlled study, I think it

does give some early hope for the device to gain some credibility and perhaps move toward FDA approval in the US, maybe allowing us to get good quality data to see if this is the right way to go for these ASD patients that we've been discussing.

Dr Ivy: So, Mary, how would this change your practice?

Dr Mullen: I think that this could be a very useful device for transcatheter closure of atrial septal defects for patients in the borderline PVR category. We frequently consider the need for a fenestration, perhaps through the ASD device sometimes; we have even positioned devices such that we leave a residual hole. Potentially the patients that have an elevated PVR—pediatric patients that maybe is older than 6, approaching 8and that respond to vasodilator testing, but that we think that we may want to leave a hole that we could go back and close later on. So, I think that it's a very useful tool.

Dr Morgan: Yes, Mary, just to follow up on that, like I said, the concept is long-standing. But I think what we've had previously is a very difficult procedure. I mean, we've done it several times, where we've placed a coronary artery stent through the material of the ASD device and tried to hope that this creates at least a medium-term persistent hole. There are many people around the world that have done that or variations on that. But I think maybe this development gives us safer, quicker, hopefully more reliable, ability to leave a fenestration in place while still reducing the overall effect of the shunt.

Dr Mullen: Oh, absolutely. There are patients that we have had fenestrations or holes that were not reliable and that we have needed to go back to recreate those holes many times in the cath lab. So, the ability to have one there right from the first closure is terrific.

Dr Farber: It would seem to me that this would potentially allow us to at least partially close people that you wouldn't consider before because you were worried about their right ventricle, even above what you're worried about in kids. Because we worry that closing this hole is going to eliminate their right ventricular pressure release and they are going to develop acute right heart failure. But this—adjustment of the fenestration might get you past that issue.

Dr Morgan: Yes, I completely agree. And again, this paper and, in fact, most of the experience that I've had with this device has been in adults. The first one of these I did was in a gentleman in his late 40s in London for exactly the reasons you mentioned. I think the interesting thing about this for me, and I think the thing that foxes many of us, is how big a hole do you leave? And although I've been interested, sitting talking to Dunbar and other people, trying to look at equations to work out pressure, decompression, and flow, looking at blood viscosity, etc, I'm still worried that we are in a position of using gut feelings to determine whether there should be a 5, a 6, or an 8 mm fenestration left. I'm going to be interested to see as practice increases whether we can get that to be more scientific or whether we are still left with gut feeling about the correct size of the residual hole. I do worry about leaving a large hole that doesn't effectively benefit the patient, because they still have a significant left to right shunt afterwards, versus a hole that closes because it's too small, doesn't allow adequate decompression, and then clots off after a couple of weeks.

Dr Ivy: Jeff, do you have any comment?

Dr Fineman: Nothing additional, I agree with what's been said. I think the ability to be able to size it reliably is very, very important.

Dr Ivy: So, I'll ask Gareth: we might see a patient with significant pulmonary vascular disease who has an atrial defect. Is there a level of shunting or another measure that you feel like that's the patient that we should consider putting in one of these fenestrated devices? How do we choose the right patient?

Dr Morgan: Well, because I am a simple plumber and not a PH specialist, I'm

not sure whether I'm the right person to answer that. But I always worry about patients who require therapy to get their shunt to a point that they justify an ASD closure. I think if we want to treat a patient with pulmonary hypertension who has a significant ASD and we find that we can increase their shunt to a pathological level with pulmonary vasodilators-and again pathological leveldoes that mean 1.6:1? Does it mean 2:1? I don't know. But I do worry about patients that require pulmonary vasodilator therapy to get them to a point where we can safely close the ASD. And I wonder, maybe it's a bit of a blanket approach, if these are the patients that we should be putting fenestrated devices into. Patients who require therapy to generate enough of a shunt to need to close should maybe have a fenestration left over, to allow their body's homeostatic mechanisms to get used to having less of a shunt while maintaining the ability to decompress if their right ventricular pressure and right atrial pressure increases.

Dr Fineman: Yes, I think that's an excellent point. I'd like to ask a question to the group, if I may. What do you use, a PVRI of 6 or 8 as operable? I mean, if you had a patient that was above that threshold initially but then got to a 6 or an 8 after a year of triple therapy, do you still think a 6 or an 8 is adequate? Or would you change that if we can't normalize this patient's resistance; maybe we should rethink this approach?

Dr Mullen: Are you talking about a 6 to an 8 at baseline, without additional change with...?

Dr Fineman: Let's say you argue that you're going to operate on anyone <8, okay? So, you have a 5-year-old VSD and their resistance is 7.8 and you're going to go ahead and operate. What if I bring you a patient the same age, who now has a resistance of 7.8 after a year of triple therapy? Would you feel the same way about that patient, or should that number be different? I know there's no data to drive that but....

Dr Mullen: I think that would be concerning. I would have hoped that there

might be some difference and would hesitate to operate.

Dr Fineman: Because there's nothing magical about the 8, right? We were in a room when we made it up. The approach that we've taken, and we've been lucky enough to get dramatic decreases with triple therapy, where they're basically normal, so we haven't really had to ask ourselves that question, but that is always in the back of my mind. I mean, I wouldn't feel comfortable with a relatively late, unrestricted VSD who we get down to 6 after a year of triple therapy. That really worries me, in terms of operability.

Dr Mullen: Yes, I would agree.

Dr Ivy: I would agree, also. I think some of the interesting papers come from countries where there are not as many therapies available. For example, in Brazil one of the main criteria they use for simple shunts is normal resting saturations and normal saturations with exercise. And I believe there's a group in India who said similar things, because of the cost to treat with these very expensive drugs and multiple re-catheterizations. I think that does make me feel more confident about recommending a surgery, if a patient during exercise does not desaturate.

Dr Mullen: Yes. But one of the things I found very interesting about the Occlutech ASD closure paper was that 63% of the patients had either bidirectional or right-to-left shunting across the fenestration at TEE post procedure, is that correct?

Dr Morgan: That's correct, yes.

Dr Mullen: So that's certainly a group of patients that you'd think when they're awake and exercising would also have some degree of desaturation. So that points to the potential use of the fenestration while exercising in that group of patients.

Dr Farber: So, to comment on what Jeff said: in my mind, an adult with an ASD who presents with a PVR of 8 versus somebody who has been on triple therapy for 1 or 2 years and decreases the PVR to 8 from a higher value is a totally different human being. Their pulmonary circulation, their pulmonary vasculature is very different from the one who has a PVR of 8 on nothing.

Dr Fineman: Right, I agree. I agree.

Dr Morgan: Can I ask you another question, guys, that's slightly related? And I'm very much being the plumber in the conversation here. Consider a patient who has an unrestricted VSD, who's got pulmonary vascular disease due to a pressure-driven VSD pathology over time? You feel that you need to close the VSD to take away the driving shunt. If you close that VSD and try and replace it, ameliorate this with an atrial communication to protect from PH crises, does that make any physiological sense at all? Does that provide any genuine reassurance? Or do you think that's treating our own paranoia? Do you think it's something that is beneficial to basically place a device that might open the atrial septum up in a patient who has been driven by a VSD physiology before?

Dr Mullen: We've done that successfully in children who are in that grey area, closing the VSD and creating an atrial communication surgically. And it's been successful in that group of patients, but I don't think there's a large series of those patients. And I would very much hesitate to do it in an older patient. You also wonder whether a patient who doesn't have a lot of tricuspid regurgitation would actually be able to utilize that as an appropriate pop-off.

Dr Morgan: Yes. Then maybe you could discuss the concept of placing a shunt in a different position? The idea of the "reverse" Potts shunt in those patients, because it fits more into the pressure-driven pathophysiology that they have in the first place. Are they better having a direct communication between their pulmonary arteries and their aorta, rather than just a diastolic flow between their atria?

Dr Ivy: So, I think one of the considerations that we're seeing, all of us, is

the Potts-or reverse Potts I guess is maybe the better way to call it—shunt is used more and more. And I think there's a certain advantage to that. One advantage is maintaining normal cerebral saturations; also having a systolic pop-off for the right ventricle. But the patients then continue to have irreversible disease. Once you create a large communication between the pulmonary artery and the aorta, then you're not going to see if it's successful, reversal of shunt to any kind of repairable situation. And that also means that you have to choose those patients wisely. So, I guess what I'm wondering is, in a patient with sub-systemic pulmonary hypertension, would you consider an atrial shunt and supra-systemic, more of a reverse Potts? Obviously, we don't know. But what's the group's thought on that?

Dr Farber: So, I can tell you, mine is fairly simple. I've been involved with just endovascular placement of it in adults with pulmonary hypertension who had failed all available therapies and, for whatever reason, were not deemed transplant candidates, and had failed IV therapy. So, this was sort of like a lastditch kind of thing.

Dr Ivy: And what were their results?

Dr Farber: The short-term results, except for one horrible case, were pretty good. The longer-term results, the numbers are small, I think I've been involved with about 6 or 7 that the long-term results have been not so great. I mean, I guess you really don't know what you're headed for and what you're comparing it to, because these are people who, for all intents and purposes, were terminal in one way or another. And some of them have survived for several years after. I assume, compared to what they would have done, that's a good outcome. But in the bigger picture, I'm not sure it is.

Dr Morgan: I think if your experience is 6 or 7 of these, my understanding is that that's actually pretty big for most people who have any interest in this. Certainly, in the congenital groups that I've taken advice from about this, there are only a handful of units I think that have got experience and most of them have done fewer than 5 patients.

Dr Farber: I mean, we actually published a series, I think there were 6 or 7 of them.

Dr Mullen: In the series 7 patients were evaluated and 4 patients underwent transcatheter Potts shunts. There was one procedural mortality and 3 patients with longer-term follow-up. One of those did well for several years post procedure and ultimately underwent transplant with preserved RV function. We've also recently performed a surgical Potts. I think for the right patient, who has clearly maximized targeted therapy, triple therapy, or whatever is tolerated for that patient, and perhaps has preservation in RV function, the reverse really is worthy of consideration.

Dr Morgan: I find it really fascinating. Again, as a plumber, I'm interested to find the correct patient who will benefit from the transcatheter Potts. But I'm cautious because having spoken to Younis Boudjemeline, who has the biggest congenital interventional experience with these, having done as many as 9 or 10. There are still a lot of parts of the procedure that we need to have a better understanding of the safest possible technique. It's still a procedure that's requiring some tweaking to make sure that we're doing it properly. And given the procedural complexity combined with the fragile patient population, I think it's going to remain a very highrisk procedure.

Dr Mullen: Yes, I agree. And I think this might be one of the groups that we really have to collect data and do very careful phenotyping to understand the time course of progression of pulmonary vascular disease in the patients themselves.

Dr Fineman: I don't have a lot of experience with the reverse Potts. You know, we talk a lot about waiting for the ideal patient. Dunbar, your comment is very interesting. In fact, we have a patient coming in who is just what you had talked about. The patient is quite symptomatic on maximal therapy but she's not quite supra-systemic. And so obviously, we're reluctant to do a reverse Potts, but wondering whether we should just open up the atrial communication. So, we have a lot of discussion about it, but I don't have a lot of personal experience.

Dr Ivy: In closing, I think observational registries may provide at least some initial thoughts as to questions to be answered or potential directions. Professor Rolf Berger is looking for new biomarkers and the Necker group in Paris is evaluating circulating endothelial cells for determining operability.

Transplantation in Eisenmenger Syndrome: Getting to the Heart of the Matter

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Pulmonary hypertension (PH) is a common complication of congenital heart disease (CHD), often developing as a result of vascular remodeling from long-standing left-to-right shunting and pulmonary overcirculation. The most severe form of CHD-associated PH is Eisenmenger's syndrome (ES), in which pulmonary vascular remodeling has led to irreversible changes, systemic pulmonary pressure, and shunt reversal, resulting in cyanosis. While the ever-increasing armamentarium of pulmonary vasodilators has given clinicians several effective treatment strategies, the disease can still progress to the point where advanced therapies such as lung transplantation, with or without heart transplantation, must be considered.

The optimal timing of transplantation in such patients is often difficult to ascertain, however, as ES patients often maintain clinical stability with favorable survival compared with pulmonary arterial hypertension (PAH) patients with similar hemodynamics. Furthermore, clinicians considering transplantation for these patients are faced with a difficult decision: to transplant the lungs only and concomitantly repair the cardiac defect, or to perform a technically less complicated heart and lung transplant.

The allure of a lung-transplant-andrepair strategy is clear: patients often have hearts that are relatively structurally healthy apart from the shunt lesion and its attendant cardiac remodeling, and should be expected to perform well after repair of the defect and relief of the afterload (high pulmonary vascular resistance) on the right ventricle (RV). Transplanting only the lungs avoids the significantly longer wait times for heartlung blocks, obviates the long-term concern of coronary allograft vasculopathy, and allows the donor heart to be used for another patient in need of this scarce resource.

Heart-lung transplants (HLT) are associated with increased mortality and morbidity compared with lung transplants alone, and, not surprisingly, the use of HLT has declined dramatically over time, from over 200 HLTs performed in 1990 to just over 50 in 2016.¹ Despite all the aforementioned advantages, however, the reality of this decision is less than straightforward; the complexities of performing cardiac repair concomitantly with a lung transplant (LT) can lead to much longer bypass times and more major bleeding complications. In fact, in a 2002 analysis of ES patients in the United Network for Organ Sharing (UNOS)/ International Society for Heart and Lung Transplantation (ISHLT) Joint Thoracic Registry who underwent either HLT or LT alone, LT was associated with worse survival than HLT, and most of this survival disadvantage occurred in the first month post-transplant, suggesting that technical and perioperative factors played an important role.² Other single-center studies have also highlighted the difficulties associated with an LT-and-repair strategy. Goerler and colleagues reported their experience

with HLT or LT for ES,³ with only 5 of 51 patients spanning 2 decades having undergone an LT-and-repair strategy, owing to the complexity of their CHD, while Ueno and colleagues reported that LT was associated with greater blood loss and worsened postoperative graft function compared with HLT, although mortality was not different by 2 years post-transplant.⁴

Clearly, a "one-size-fits-all" approach is inappropriate in this patient population; the question, then, is which patients should be treated with HLT, and which patients can be successfully managed with LT and repair of the cardiac defect? While this question is far from definitively answered, we do have some clues. In general, the more complex the cardiac repair, the less successful an LT-and-repair strategy is likely to be, as longer ischemic times associated with a complex repair are likely to lead to ventricular diastolic dysfunction; one group suggested that HLT be performed rather than LT in any patient in whom the cardiac repair is expected to take more than 60 minutes.⁵ Curiously, in the above-mentioned UNOS analysis, while patients whose underlying cardiac defect was a ventricular septal defect (VSD) had better post-transplant outcomes than those with an atrial septal defect (ASD) or patent ductus arteriosus (PDA), the association between a lung (rather than heart-lung) transplant strategy and poorer outcomes was strongest among VSD patients. The reasons for this are

not entirely clear, as data concerning the specific anatomy of the VSDs or their repairs are not available; however, 5 deaths in the LT arm were due to ventricular failure, while no such deaths were reported in the HLT arm, suggesting that perhaps the recipient heart was not as healthy as expected in these cases. Toyama and colleagues reported 2 cases of ES treated with an LT-and-repair strategy⁶; in the first, the underlying cardiac lesion was an ASD and the postoperative course was complicated by significant left ventricular diastolic failure, manifested by elevated pulmonary capillary wedge pressure and severe pulmonary edema requiring prolonged extracorporeal membrane oxygenation (ECMO) and ventilator support. The second case involved both a VSD and an ASD, where no such difficulty was experienced. The left ventricle (LV) in the first case was extremely diminutive, squashed by the much larger, dilated RV, whereas the LV in the second case was normal in size, presumably attributable to the volume load initially imposed by the VSD. The authors postulate that the chronically underfilled LV in the first case was less able to accept the increase in preload after relief of RV afterload.

Clearly, making definitive conclusions regarding the optimal treatment strategies for these complex patients is not currently possible; ultimately, decision-making remains a highly individualized process that needs to incorporate the complexity of the congenital lesion and associated repair, patient comorbidities, and the experience of the transplant team.⁷ Currently, the evidence and collective experience suggest that HLT is an excellent treatment strategy with acceptable outcomes and should probably be the strategy used for most CHD patients with ES. However, an LTand-repair strategy could be considered for patients with lesions for which the repair is likely to be straightforward and relatively quick, such as simple ASDs, PDAs, and the most straightforward perimembranous VSDs. Patients with any evidence of structural or functional abnormalities of the LV should be approached with particular caution when considering an LT-and-repair strategy, as postoperative ventricular failure can be disastrous.

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Eisenmenger Syndrome: When Less Is More

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Presentation: A 61-year-old woman with Eisenmenger syndrome due to an unrepaired truncus arteriosus (type 2) and a history of atrial fibrillation complicated by a cerebrovascular accident presented to an outside hospital with one week of worsening exertional shortness of breath, cough, and chills after recent airplane travel to the Philippines. She had been managed at our pulmonary hypertension center for 5 years and treated with sildenafil as well as warfarin for her history of atrial fibrillation. Evaluation at the outside hospital included a chest radiograph showing a left lower lobe infiltrate. She was started on a continuous heparin infusion for possible pulmonary embolism, as her international normalized ratio was subtherapeutic at 1.6. She was also started on ceftriaxone and doxycycline before transfer to our tertiary care center for further management.

Physical examination at the time of her arrival revealed a chronically ill– appearing woman with increased work of breathing. She was normotensive, tachycardic, and resting pulse oximetry saturation was 84% to 85% on 5 liters of supplemental oxygen; at baseline she used 2 liters of supplemental oxygen with oxygen saturations in the mid-80s. Auscultation revealed decreased breath sounds bilaterally with diffuse expiratory wheezing, a loud S2, and a III/VI systolic murmur heard loudest at the left upper sternal border. Extremities had decreased pulses bilaterally, clubbing of all digits, and 1+ edema to the midshins.

Prior Medical History: The patient was diagnosed with truncus arteriosus after presenting with tachypnea at a few days of life. It was recommended that she undergo heart surgery, but her parents declined due to lack of surgical expertise in their hometown. The patient had multiple hospitalizations during infancy and childhood for congestive heart failure but eventually improved, likely due to the development of pulmonary vascular disease. She survived a pregnancy and delivery at 28 years of age in

the Philippines. Since then she reported progressive dyspnea, perioral and digital cyanosis, and fatigue. She was diagnosed with paroxysmal atrial fibrillation and started on warfarin. In 2010 she had dysmenorrhea for which she underwent a uterine biopsy and suffered a cerebrovascular accident when warfarin was held perioperatively. She has mild residual left hand and arm weakness.

In 2013 she underwent diagnostic cardiac catheterization showing a pulmonary artery pressure (PAP) of 145/61 mm Hg with a mean of 95 mm Hg and an indexed pulmonary vascular resistance (PVRi) of 58 Wood units per meter squared of body surface area. Supplemental oxygen resulted in a decrease in PVRi to 23 Wood units per meter squared and the addition of inhaled nitric oxide (iNO) reduced the PVRi to 14.4 Wood units per meter squared. She also was noted to have a single coronary artery arising from the anterior aspect of the left sinus of Valsalva. She was started on oral sildenafil 20 milligrams 3 times daily with significant improvement

in symptoms and decreased cyanosis. She was then started on ambrisentan 5 milligrams orally once daily with development of pedal edema and abdominal bloating. The ambrisentan was discontinued and supplemental oxygen was started. Her 6-minute walk test (on room air) after 3 months of treatment demonstrated desaturation from 80% at rest to as low as 57% with ambulation after 2 minutes of walking. After one year of treatment she remained functionally impaired, again walking for only 2 minutes but with resting oxygen saturation of 87% falling to only 68% with ambulation.

Hospital Course: The patient was admitted to the cardiac intensive care unit and continued on anticoagulation and antibiotics. Chemistries and arterial blood gas showed an acute-on-chronic respiratory acidosis. Coagulation studies showed subtherapeutic international normalized ratio and partial thromboplastin times, and complete blood count showed an elevated white blood cell count to 10,000/uL with a hemoglobin of 18.3 g/dL and a hematocrit of 55.9%. Respiratory pathogen PCR panel was positive for respiratory syncytial virus. A chest radiograph showed moderately enlarged central pulmonary arteries but did not reveal an acute cardiopulmonary process. Transthoracic echocardiogram demonstrated unrepaired truncus arteriosus and a large, unrestrictive perimembranous ventricular septal defect with bidirectional flow, a dilated right ventricle with severe hypertrophy and mild to moderately reduced systolic function, flattening of the interventricular septum throughout the cardiac cycle, right atrial dilation, an estimated right ventricular systolic pressure of at least 98 mm Hg, normal left ventricular size and systolic function, a thickened truncal valve with a peak gradient of 21 mm Hg, and no other valvular disease. Lower extremity venous Doppler ultrasounds were negative for deep venous thrombosis. CT angiogram chest showed no pulmonary embolism but did show centrilobular ground glass opacities, worse in the right lung, and near collapse of the left lower lobe with superior segment sparing.

The patient was initially treated with iNO at 10 ppm and inhaled iloprost 5 micrograms every 4 hours. She was maintained on her home dose of sildenafil to achieve pulmonary vasodilation and continued on ceftriaxone and doxycycline for presumed community-acquired pneumonia. Her oxygen saturations continued to deteriorate, ranging from 50% to 70% on maximum noninvasive support. She was started on a combination of intravenous dobutamine and phenylephrine for improved pulmonary blood flow and systemic blood pressure support. Her antimicrobial coverage was broadened to vancomycin and meropenem, but her oxygen saturations did not improve. She had several episodes of melena and hematochezia with hemoglobin levels falling to 10 to 11 g/dL. Imaging of the gastrointestinal tract with an esophagogastroduodenoscopy was thought to be too high risk. Her hemoglobin goal was increased to 16 g/dL in an attempt to increase her oxygen carrying capacity and she received a total of 7 units of packed red blood cells over 10 days. This resulted in a significant improvement in her clinical status. She was also diuresed with intermittent doses of intravenous furosemide. She was progressively weaned from the iNO, iloprost, and inotropic support and transitioned from high-flow nasal cannula supplemental oxygen to 3 liters of supplemental oxygen with saturations in the mid to high 80s. She was discharged from the hospital after one month in the intensive care unit on sildenafil 20 milligrams 3 times daily as she was intolerant of higher dosing due to intermittent hypotension, warfarin, and 2 to 3 liters of supplemental oxygen.

Six months following this hospitalization she underwent repeat cardiac catheterization. On room air her PAP was 142/53 mm Hg with a mean of 85 mm Hg and a PVRi of 28.4 Wood units per meter squared. She is awaiting initiation of macitentan and has been advised to undergo evaluation for heart and lung transplantation.

Discussion: Truncus arteriosus (TA) is a rare form of cyanotic congenital heart disease (CHD), affecting 1 in 10,000 live births and accounting for

approximately 1% of congenital heart lesions.¹ TA occurs due to failure of the development of the conus arteriosus, which normally separates the primitive truncal valve into the aortic and pulmonary valves. In the absence of a conus arteriosus and spiral septum, there is a nonrestrictive outflow ventricular septal defect with blood ejected from both ventricles across a common truncal valve into the truncus arteriosus. The pulmonary arteries then emerge in a series of ways, either from the ascending aorta as a common trunk (type 1) or less often arising separately from the ascending truncus (type 2). The natural history of unrepaired TA is dismal, with death in early infancy usually secondary to heart failure and a survival of only 15% at one year of age. Those patients who survive to young adulthood will unequivocally develop pulmonary arterial hypertension (PAH),² with subsequent mortality attributed to complications of pulmonary vascular disease and infective endocarditis.3

Uncorrected CHD frequently results in PAH, the most severe form of which is Eisenmenger syndrome (ES). Unrepaired systemic-to-pulmonary communications cause pulmonary vascular remodeling secondary to nonrestrictive increases in pulmonary blood flow and PAP.⁴ Over time, as pulmonary arterial resistance exceeds that of the systemic vasculature, the shunt direction reverses resulting in predominant right-to-left flow and oxygen-unresponsive hypoxemia. This stage, identified as ES, represents a disease state in which pulmonary hypertension is largely irreversible and cardiac lesions are inoperable.⁵ Although the prevalence of ES is not known, historical data estimate that approximately 11% of patients with CHD with known left-to-right shunts develop ES.⁶ Although natural history studies of ES patients have demonstrated a wide spectrum of variability, survival overall is thought to be superior to other forms of PAH, with approximately 95% survival at 5 years and 56% at 20 years following ES diagnosis.⁷

The majority of patients with ES survive to adulthood. Their clinical course, however, is complicated by the development of a unique constellation of multisystem disease that does not occur in idiopathic PAH (IPAH) including coagulopathy, erythrocytosis, hyperviscosity, renal dysfunction, pulmonary hemorrhage/hemoptysis, endocarditis, and brain abscesses.⁸ Though our patient has a history of menorrhagia and ischemic stroke in the setting of atrial fibrillation, she has otherwise been without other multisystem sequelae of ES. It is important to note that this complex profile includes both a tendency toward bleeding and clot formation, with proximal pulmonary artery thrombosis observed in 21% to 29%, and distal pulmonary artery thrombosis observed in 43%, of patients with ES.^{9,10} Women and patients with lower oxygen saturations were noted to be at increased risk for pulmonary embolism. While most clinicians recommend anticoagulation for ES patents who have experienced a pulmonary embolism, there are no data to support routine prophylactic anticoagulation in this patient subset as it has not been shown to impact long-term survival.¹¹ The risk of hemoptysis and absence of a consensus international normalized ratio target range for ES patients add to the complexity of routinely anticoagulating these patients.

Despite the consequences of chronic cyanotic heart disease enumerated above, ES patients were historically thought to have slower disease progression and overall improved survival compared to their IPAH counterparts.¹² This was thought to be secondary to a "training effect" on right ventricular function in the setting of long-standing right ventricular hypertension and the inherent benefit of a right-to-left shunt in relieving these elevated right ventricular pressures. This survival advantage in ES patients, however, is challenged by more recent data from REVEAL (Registry to Evaluate Early and Long-Term PAH Disease), which demonstrated higher systemic blood flow, lower mean right atrial pressure, higher mean PAP, higher pulmonary vascular resistance index, and lower systemic arterial saturations at rest in ES patients compared to those with IPAH, and also found no difference in 4- or 7-year survival between these patient cohorts. Within the ES cohort, superior 6-minute walk time, lower mean right atrial pressure and brain natriuretic peptide level, and more acute pulmonary vasoreactivity was associated with a survival advantage.¹³ These data highlight the unique hemodynamic profile of ES patients which, despite similar pulmonary vascular histopathologic changes to patients with IPAH, complicates empirical extrapolation of IPAH therapies to the ES population.

Investigation of targeted PAH agents for ES has been limited partly due to concern for increased right-to-left shunting and worsened hypoxemia in the context of systemic vasodilation precipitated by these agents. BREATHE-5, the first placebo-controlled study in ES, demonstrated that bosentan significantly improved 6-minute walk distance and reduced PVRi without worsening oxygen saturation.¹⁴ Long-term analysis of the data also highlighted the dynamic nature of ES as PVRi increased in the placebo arm and improvements in functional status persisted beyond the end of the bosentan treatment window.¹⁵ Treatment with sildenafil improved pulmonary hemodynamics (reduced systolic and mean PAPs, lower pulmonary vascular resistance, and improved pulmonary arterial saturation) in ES patients.¹⁶ Subsequent studies also demonstrated a significant improvement in quality of life and functional capacity in ES patients treated with sildenafil.¹⁷ The newly updated American College of Cardiology/American Heart Association (ACC/ AHA) Guideline for the Management of Adults with Congenital Heart Disease offers lesion-specific guidance for initiation of PAH treatment in ES, with bosentan as a Class I indication for ES secondary to an atrial or ventricular septal defect and combination therapy of bosentan and/or sildenafil as a Class IIa recommendation for all forms of symptomatic ES.¹⁸ Although small in size, additional studies have shown improvement in exercise capacity in ES patients treated with ambrisentan and macitentan.^{19,20}

As the studies above demonstrate, ES patients often respond favorably to advanced PAH therapies despite long-standing pulmonary vascular disease. This may be due, in part, to

maintenance of pulmonary vasoreactivity in ES patients that was also seen in our case presentation patient.^{21,22} Although our patient was a notable outlier given her survival to an advanced age with unoperated TA, it is intriguing to hypothesize that her improved survival was, in part, due to retained plasticity of her pulmonary vasculature. Although most prior studies, including REVEAL, have demonstrated poor vasodilatory response testing in the ES population (8% vs 22% in iPAH),¹³ a few studies have shown that approximately 20% to 30% of ES patients respond to nitric oxide inhalation (defined as a 20% reduction in PVR); they have improved survival (90% vs 40% at 10 years) and freedom from treatment with prostacyclin-based therapy or heart-lung transplantation compared to their ES counterparts that are "nonresponders."²³ It is important to note that the definition of a responder in this study was not as strict as those proposed by Sitbon et al (reduction in mean PAP of ≥10 mm Hg, reaching an absolute value of mean PAP ≤40 mm Hg, with unchanged or increased cardiac output) and adopted by the ACC/AHA and European Society of Cardiology for pulmonary hypertension.^{24,25} This finding, however, highlights the benefit of early testing of the reactivity of the pulmonary vasculature in ES patients to provide a tailored approach to care. Further work remains in defining the unique anatomic, hemodynamic, and clinical characteristics that exist even within the ES population and defining the optimal treatment approach for this complex subset of PAH patients.

Teaching Points

- 1. ES is a complication of CHD associated with unrepaired systemic to pulmonary shunts that result in increased PAP and eventual reversal of the shunt direction.
- 2. Patients with ES may develop unique multisystem disease including coagulopathy, erythrocytosis, hyperviscosity, renal dysfunction, pulmonary hemorrhage/hemoptysis, endocarditis, and brain abscess that is not characteristic of other forms of pulmonary hypertension.

- 3. Although patients with ES are at high risk for pulmonary artery thrombosis, prophylactic anticoagulation has not been shown to improve survival and is not recommended as part of routine care.
- 4. Retained pulmonary vasoreactivity occurs in 20% to 30% of ES patients and is associated with improved survival.
- 5. Evidence for targeted pulmonary hypertension therapy in ES is emerging. Bosentan and sildenafil are recommended treatments for ES in the new ACC/AHA 2018 Guideline for the Management of Adults with Congenital Heart Disease.

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Comprehensive Evaluation and Ongoing Approach to Children With Down Syndrome Who Have Pulmonary Hypertension or Are at Risk of Developing Pulmonary Hypertension

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Children with Down syndrome and pulmonary hypertension (PH) are a unique and challenging group of patients. Down syndrome, or Trisomy 21, affects approximately one in every 600 to 800 live births.¹ PH, currently defined as a resting mean pulmonary artery pressure of ≥ 25 mm Hg, is known to increase morbidity and mortality significantly in this group of patients and has been identified in as many as 28% of all patients with Down syndrome. Furthermore, specific risk factors and comorbidities have been shown to increase the chance of developing PH in this population.² Careful screening and proper treatment is imperative in children with Down syndrome to prevent the development, recurrence, or progression of PH in this population.

Recent findings from Bush et al demonstrate clear clinical characteristics and risk factors for development of PH in children with Down syndrome.² Prior to this study, data regarding the incidence of PH throughout the Down syndrome lifespan, associations with comorbidities, exacerbating factors, and overall impact of PH in the Down syndrome population were lacking. Most notably, perhaps, was their finding that a vast majority (87%) of patients who suffered from recurrent PH after a previous resolution were classified as World Health Organization (WHO) Group 3 or associated with lung disease. The

study also demonstrated that obstructive sleep apnea (OSA), recurrent hypoxia, and aspiration are clear risk factors for development or recurrence of PH. Given these findings, we as providers must take an organized approach in screening for potentially preventable lung insults that contribute to the development and further progression of PH.

CLASSIFICATION AND INCIDENCE

It is well known that PH in children with Down syndrome is most frequently classified as Group 1 PH (PAH, pulmonary arterial hypertension) associated with congenital heart disease (CHD) or persistent pulmonary hypertension of the newborn (PPHN), and oftentimes a combination of the two.^{2,3} For one cohort of children with Down syndrome followed prospectively in the Netherlands, 5.2% had PPHN, which is significantly higher than the reported 0.1% in the general population.³ In the large group of children followed in the Down Syndrome Clinic at Denver Children's Hospital (n=1252), of the 28% identified as having PH, 82% had associated CHD and 45% had PPHN.² The most common cardiac congenital malformations associated with Down syndrome include atrioventricular canal, patent ductus arteriosus, atrial septal defect, and ventricular septal defect, all of which

include cardiac shunts that can lead to PH due pulmonary over circulation.^{2,3,10} The American Academy of Pediatrics (AAP) recommends an echocardiogram in the first month of life for all babies with Down syndrome; therefore, most are diagnosed and repaired in infancy.⁵

While cardiopulmonary abnormalities including CHD and PPHN are the most common etiology of PH onset in infancy, lung disease is the more common etiology seen after infancy or with recurrent disease. It appears that PH develops more readily from hypoxia in the Down syndrome population, and that children with a prior diagnosis of PH are more likely to develop a recurrence of disease in the context of a respiratory comorbidity such as OSA, intermittent hypoxia, recurrent pneumonia, and chronic aspiration. Given the high rate of respiratory comorbidities in these children, it is not surprising that 87% of children experiencing a second episode of PH after a previous resolution were classified as WHO Group 3.² For any patient with Down syndrome and PH (or history of PH), a primary pediatric pulmonologist should be identified and follow the patient along with the PH team indefinitely.

For those Down syndrome patients who have resolution of their PH, it is imperative they have regular screening for comorbid respiratory conditions despite the presence or absence of symptoms. Given what we know about this population, we are empowered to prevent the recurrence of PH in this high-risk population by continuing to regularly screen for respiratory comorbidities, rather than screening only after echocardiogram evidence of PH becomes apparent.

FREQUENT COMORBID CONDITIONS

Aspiration

A frequently overlooked cause of PH and other respiratory symptoms in Down syndrome is unrecognized aspiration. Children with Down syndrome are at significant risk for chronic aspiration due to delayed oral development, structural abnormalities, and hypotonia.¹ One study of patients with Down syndrome followed in a sleep clinic in the United Kingdom showed 16/17 computerized tomography (CT) scans done on this population revealed findings suggestive of aspiration.⁴ In the Denver cohort, 35% of all patients with Down syndrome with PH were reported to have chronic aspiration. That number increased to 48% of patients with recurrent PH, highlighting the significant role chronic aspiration can play in children with a history of PH.² The AAP recommends video fluoroscopic swallow study (VFSS) for any child with Down syndrome with "marked hypotonia, slow feeding, choking with feeds, recurrent persistent respiratory symptoms, or failure to thrive" in the first year of life. They do not provide recommendations for any routine screening.⁵ We recommend that a VFSS be performed for all children with Down syndrome, despite a presence or absence of aspiration symptoms, as part of the initial comprehensive evaluation for new PH diagnosis, recurrence of previously resolved PH, poorly controlled or worsening PH, and periodically for those with a history of diagnosed aspiration. All patients with presumed or confirmed aspiration should by regularly followed by a feeding therapist as well as a pulmonologist for ongoing assessment and monitoring.

Obstructive Sleep Apnea

There is a significant risk of OSA, found in multiple studies to be present in anywhere from 30% to 79% of all patients with Down syndrome (compared with just 2% of the general pediatric population).^{1,2} In the Denver cohort of patients with Down syndrome, 78% of those with PH were also diagnosed with OSA, showing an incredibly high association of the two diseases.² Because of the known risk factor of OSA in the Down syndrome population, the AAP recommends a sleep study by age 4 years for all children with Down syndrome, and sooner if one exhibits signs or symptoms of sleep-disordered breathing.⁵ However, as McDowell explains, relying on parental report is somewhat problematic. Parents of children with Down syndrome consistently underestimate the presence of sleep-disordered breathing. In one study, 69% of parents of children with Down syndrome denied any sleep problems, yet 54% of those same children had abnormal sleep study findings.⁶ Because of this, we recommend a standardized approach for screening for OSA in patients with history of PH or active disease, instead of determining need based on parental report.

For those children with a new diagnosis of PH (or new recurrence), a sleep study should be done as part of initial comprehensive workup, as is recommended with any child with new diagnosis of PH (not just patients with Down syndrome).⁷ For those with a history of resolved or controlled PH, we feel it is reasonable to be assessed in a sleep clinic annually so that the specialists in that clinic help determine the need for and frequency of sleep studies. And finally, in PH patients with Down syndrome who have lack of improvement or clinical worsening despite optimal PH treatment, sleep studies should be repeated every 1 to 2 years given the high rate of association of OSA and PH. Providers commonly assume that pediatric patients with Down syndrome have low adherence to prescribed respiratory support, and sometimes resist repeating sleep studies if they do not believe their patients will comply with recommendations. However, a recent study showed more than half of children (22/39)had satisfactory and regular usage of prescribed respiratory support, further emphasizing the need for ongoing OSA

screening.⁴ While adenotonsillectomy can improve sleep-disordered breathing in this population, underlying airway structure or dynamics may cause significant residual OSA. Because of this, reassessment after surgery is also imperative.¹

Parenchymal and Structural Airway Disease

Children with Down syndrome are known to have an increased incidence of pulmonary abnormalities when compared to the general population. Common airway abnormalities include anomalies such as macroglossia, tonsil and adenoid hypertrophy, laryngomalacia, tracheobronchomalacia, subglottic stenosis, and tracheal stenosis.¹ These airway abnormalities predispose patients to intermittent hypoxia, which can lead to the development of PH in this at-risk population. In one review, approximately 50% of patients with upper airway obstruction had PH documented by echocardiogram or cardiac catheterization, with 91% resolution of PH following surgery.⁸ While we know patients with Down syndrome can also have primary parenchymal lung disease (such as pulmonary hypoplasia, pulmonary lymphangiectasia, lymphoid interstitial pneumonitis, and other interstitial lung disease), they are more likely to have diffuse parenchymal disease from secondary causes such as postinfectious changes, chronic lung disease of prematurity, and chronic aspiration. Interestingly, there are significantly lower rates of asthma in the Down syndrome population, which should prompt the provider to screen for alternative causes of coughing and wheezing.¹

These well recognized comorbidities highlight the importance of proper screening for pulmonary abnormalities, including advanced imaging with high-resolution chest CT at the time of PH diagnosis or recurrence, and need for good, ongoing pulmonary specialty care. Furthermore, it is has been shown that patients with Down syndrome may not respond to pulmonary vasodilators in the same way as patients without Down syndrome, potentially indicating that ongoing pulmonary (or other) insults have not been properly identified or treated correctly prior to initiation of PH-specific Table 1. Seattle Children's Hospital screening guidelines for children with Down syndrome and PH or at risk of developing PH

	AAP standard of care for all patients with Down syndrome	Any child with chronic respiratory conditions	New PH diagnosis or recurrent episode	PH resolved or well controlled	No improvement in PH / worsening
Echocardiogram	First month of life	Consider screening for PH every year	With initial evaluation	Annually until school age for resolved PH (CHD, PPHN, or other cause PH) At least annually indefinitely for well- controlled PH	As frequent as PH team suggests
Pulmonology consult	N/A	Evaluation by pediatric expert and continue to follow regularly	With initial evaluation if not previously established	Continue to follow regularly until lung disease r/o as contributing factor	Continue to follow regularly until lung disease r/o as contributing factor
VFSS	In first year of life only if symptoms present	As soon as respiratory symptoms become apparent	With initial evaluation	Annual evaluation by speech therapist and VFSS until age 6 years; consider annual screening thereafter for those with history of diagnosed aspiration	At least annually (more frequent if unexplained worsening)
Sleep study	By age 4 years	Per primary pulmonologist	With initial evaluation	Consider annual sleep clinic evaluation	Annually repeat after any surgical airway management
Chest CT	N/A	Should be strongly considered	With initial evaluation	N/A	Consider repeating at intervals decided with primary pulmonologist to screen for ongoing evidence of aspiration, other parenchymal disease, or pulmonary venous obstruction
Lab surveillance: BNP, Thyroid, ANA	Thyroid: NB, 6 months, 12 months, annually	Consider BNP with echo screening	With initial evaluation	At least annually	At least annually. BNP more frequently to trend response to treatment

therapy.⁹ The Pediatric PH Guidelines from the American Heart Association and American Thoracic Society also highlight the importance of identifying and treating primary or secondary respiratory disease prior to the initiation of long-term pulmonary vasodilator therapy.⁷

CONCLUSION

Given what we currently know about Down syndrome and PH, our PH center at Seattle Children's Hospital has developed guidelines and standards of care for the patient with Down syndrome throughout their lifespan (Table 1). Both inpatient and outpatient PH referrals too often come after months to years of unrecognized pulmonary insults. With proper education and reinforcement of proposed guidelines for screening, our hope is that comorbidities are recognized and treated prior to the development of or worsening of PH, ideally prior to referral to the PH center, but certainly as part of the ongoing, comprehensive care of the child with Down syndrome and PH.

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