Research Article

Pulmonary Circulation

The impact of right ventricular pressure and function on survival in patients with pulmonary vein stenosis

Michelle C. Sykes[1], Christina Ireland[2], Julia E. McSweeney[2], Emily Rosenholm[2], Kristofer G. Andren[1] and Thomas J. Kulik[1,3]

[1]Department of Cardiology, Boston Children's Hospital, Boston, MA, USA; [2]Cardiovascular Nursing Patient Services, Boston Children s Hospital, Boston, MA, USA; [3]Pulmonary Hypertension Program, Boston Children's Hospital, Boston, MA, USA

Abstract

Pulmonary vein stenosis (PVS) is associated with pulmonary hypertension (PH), but there is little information regarding the impact of PH on right ventricular (RV) systolic function and survival. We conducted a retrospective cohort study of our patients to explore this and other aspects of pulmonary hemodynamics with PVS. RV function was assessed using qualitative two-dimensional echocardiography. The ratio of systolic pulmonary artery (PA) and aortic pressures (PA:Ao) at cardiac catheterization reflected pulmonary hemodynamics. Reactivity testing employed inhaled nitric oxide + 100% fiO_2, or 100% fiO_2 only; "reactivity" was a $\geq$ 20% decrease in PA:Ao.

There were 105 PVS patients, although not all had data at every time point. (1) The mean PA:Ao at first cardiac catheterization (n = 77) was 0.79 ± 0.36; at last catheterization (n = 54), PA:Ao = 0.69 ± 0.30; 90% had systolic PAP > one-half systemic. Survival was shorter with PA:Ao > 0.5. (2) Differences in survival relative to RV dysfunction on the first echocardiogram were not significant, although they were using the last echocardiogram. (3) The magnitude of RV dysfunction was positively correlated with PA:Ao. (4) Balloon dilation of PV acutely decreased PA:Ao (-0.13 ± 0.37, $P = 0.03$ [n = 40 patients]). 5. Of 20 patients tested, 13 were acutely reactive to vasodilators.

PH is a major feature of PVS. Reduced RV function and PA:Ao appear to be predictors of survival. Given the importance of PH in this disease, clinical studies of PVS treatments should include measures of PAP and RV function as important variables of interest.

Keywords

pulmonary hypertension, pulmonary venous hypertension

Date received: 8 January 2018; accepted: 22 April 2018

Pulmonary Circulation 2018; 8(2) 1–6
DOI: 10.1177/2045894018776894

It has been known since the 1950s that pulmonary vein stenosis (PVS) is associated with pulmonary hypertension (PH),[1,2] and multiple reports documenting pulmonary arterial pressures (PAP) with this condition have been published since.[3–7] However, very little information is available with respect to the impact of PAP or the ratio of PAP to systemic blood pressure[8] on right ventricular (RV) systolic function, survival, and clinical course. PVS patients are complex, variably exhibiting not only PH but also abnormal pulmonary parenchyma, abnormal distribution of pulmonary perfusion, and increased lung water. Understanding the impact of PH may help better define the pulmonary vascular contribution to the phenotype of these patients and may be of prognostic value. Recent interest in trying new approaches to treat this difficult disease[9] emphasizes the need to develop

Corresponding author:
Thomas J. Kulik, Boston Children's Hospital, Department of Cardiology, Division of Cardiac Critical Care, and the Pulmonary Hypertension Program, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.
Email: thomas.kulik@cardio.chboston.org

a more complete appreciation of the complex pathophysiology involved.

We therefore conducted a retrospective cohort study of patients with PVS seen at our institution to determine the relationship between PAP, RV systolic function, and survival. We also investigated the effect of pulmonary vein (PV) balloon dilation on pulmonary vascular hemodynamics and the acute response to inhaled vasodilators.

Methods

The Boston Children's Hospital (BCH) PVS registry was used to identify patients evaluated for PVS during 2000–2015. Echocardiography and cardiac catheterization reports, along with hospital clinical records relevant to the patients' diagnoses, medications, and clinical course, were examined. This study was approved by the Boston Children's Hospital Institutional Review Board.

All patients in this report had two ventricle physiology and ≥ 2 affected (stenotic or atretic) PVs at some point in their course. Patients had one of four types of PVS: idiopathic; associated with congenital heart disease (any cardiac defect save for hemodynamically insignificant patent foramen ovale, small atrial septal defect or small patent ductus arteriosus); associated with prematurity and bronchopulmonary dysplasia; or following repair of total anomalous pulmonary venous connection. Therapeutic modalities used to treat PVS varied during the 15-year interval and included: PV balloon dilation ± stenting; operative palliation (sutureless "repair" or resection of stenosis); and atherectomy; adjunctive chemotherapy included vinblastine, methotrexate, bevacizumab, and imatinib.

Cardiac catheterizations were generally conducted with the patient intubated and under general anesthesia; intravenous vasoactive agents were sometimes used to support the circulation during the catheterization.

RV systolic function was assessed using two-dimensional (2D) echocardiography, subjectively graded (by an attending cardiologist specializing in echocardiography) as having normal or mildly, moderately, or severely depressed function. Because pulmonary vascular resistance cannot be calculated as PV pressures often vary from vein to vein, we used the ratio of systolic PA to systolic aortic pressure (PA:Ao) to reflect pulmonary hemodynamics. Echocardiograms and cardiac catheterization reports were reviewed from the first and last encounter at BCH. For comparison of PA:Ao to RV function, only patients for whom these variables were measured < 5 days apart were included. Reactivity testing was performed using inhaled nitric oxide (iNO), 20–80 ppm + 100% fiO_2, or 100% fiO_2 only. Being "reactive" was defined as a $\geq 20\%$ decrease in PA:Ao with exposure to the dilator gases. This definition is not consistent with established criteria for reactivity, which requires measurement of pulmonary blood flow, but was used in part because few of our patients had this measured before and during vasodilator administration.

Continuous variables are summarized as medians with range or 25th and 75th percentiles as noted; categorical variables are presented as frequencies and percentages. Continuous measurements before and after catheterization are presented as mean ± SD and comparisons were performed using a paired t-test. Correlations between ordinal variables were evaluated using the Spearman correlation coefficient. Time from catheterization or echocardiogram until death is estimated using the Kaplan–Meier method; survival times are compared using the log-rank test.

Results

There are 105 PVS patients in the cohort. See Table 1 for patient characteristics. The patients with congenital heart disease (not including those having had total anomalous pulmonary venous connection repair) had these diagnoses: complete atrioventricular canal defect (n = 10); ventricular septal defect ± atrial septal defect ± patent ductus arteriosus (n = 8); complex heart disease (n = 8); atrial septal defect, including incomplete atrioventricular canal defect (n = 3); truncus arteriosus (n = 2); coarctation of the aorta ± ventricular septal defect (n = 2); partial anomalous pulmonary venous connection (n = 2); and pulmonary valve stenosis (n = 1).

Please note that patients had a variable number of hemodynamic and echocardiographic studies and as a result sample sizes differ for each sub-cohort analysis. Our key findings are:

(1) The mean PA:Ao at first interventional cardiac catheterization at BCH (before any intervention) (n = 77) was 0.79 ± 0.36; at last catheterization (n = 54), PA:Ao = 0.69 ± 0.30. Seventy-eight percent of our patients had systolic PAP > one-half systemic at the initial catheterization (Table 2). Time to death was shorter for patients with PA:Ao > 0.5 at initial and last cardiac catheterizations (Figs. 1 and 2). We also related the change in PA:Ao between the initial and last catheterizations to survival; although there was a trend suggesting improved survival with a fall in PA:Ao, this was not statistically significant ($P = 0.45$) (Fig. 3).
(2) Table 2 gives the distribution of RV systolic function. Differences in time to death relative to RV function on the first echocardiogram were not statistically significant, although they were using the last echocardiogram (Fig. 4).
(3) At the time of the first cardiac catheterization, the magnitude of RV dysfunction was positively correlated with PA:Ao (Table 3).
(4) Although high PA:Ao and reduced RV function were associated with reduced survival in the aggregate, there were exceptions, and we sought explanation(s) for this. Seven patients died in the first year of life despite normal RV function on their first echocardiogram; while we could not determine the precise causes of death, four

Table 1. Characteristics of PVS patients in the entire cohort (n = 105 unless otherwise noted).

Variables (n = 105 unless otherwise noted)	Median (25th–75th percentiles), [range]	%
Age at diagnosis (months)	5.3 (2.8–9.2) [0–304 days]	
Male gender		55
≥ 37 weeks gestation*		55
Type of PVS		
Idiopathic		21
BPD		13
CHD		34
TAPVC (post-repair)		31
Affected PV at initial diagnosis (n)		
1		11
2		22
3		30
4		29
5		8
6		1
overall	3 (2–4) [1–6]	
Surgical PV interventions (n = 98)	1 (1–1) [0–3]	
Catheter PV interventions (n = 96)	3 (1–6) [0–24]	
Time from first to last cath. (years) (n = 62)	0.7 [1 day–7]	
Time from first cath. to last follow-up/death (years) (n = 84)	1.3 [4 days–8.6]	
Time from last cath to last follow-up/death (years) (n = 62)	0.2 [0 days–7.1]	
Targeted PH therapy (n = 105)		
Sildenafil		32
≥ 3 mg/kg/day		11
Bosentan		1
Remodulin		1
Lost to follow-up		4
Still alive		61

had complex medical problems (a history of prematurity, chronic lung disease, multiple congenital anomalies, congenital heart disease) which presumably contributed to their deaths. In three patients, PVS appeared to be the most significant problem. Conversely, of patients with initial PA:Ao ≥ 1.0, 4/9 were still alive at the age of three years: two had dropped their PA:Ao to < 1.0 and had normal RV function; one still had systemic PAP but normal RV function; one still had PA:Ao > 1.0 and severe RV dysfunction, and died early in his fourth year of life.

(5) Balloon dilation of one or more PV acutely decreased PA:Ao. Combining both initial and last catheterizations, 40 patients had PA:Ao measurements before and immediately after dilation; the change in Pa:Ao was

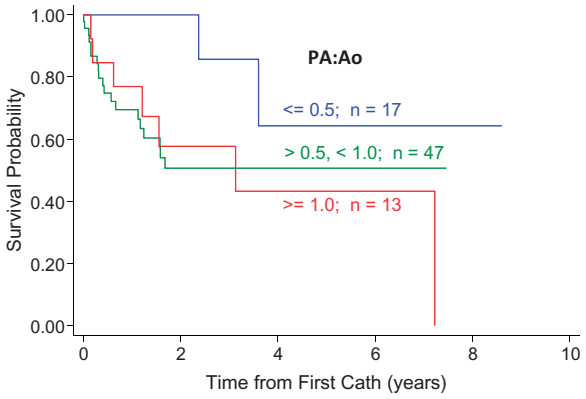

Fig. 1. Time to death tends to shorten as PA:Ao increases, initial measurement of PA:Ao. n = the number of patients at the initial catheterization. log-rank $P = 0.05$.

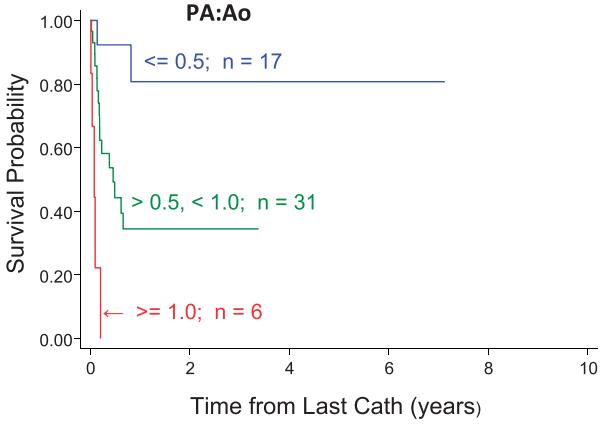

Fig. 2. Time to death tends to shorten as PA:Ao increases, last measurement of PA:Ao. n = the number of patients at the last heart catheterization; log-rank $P < 0.001$.

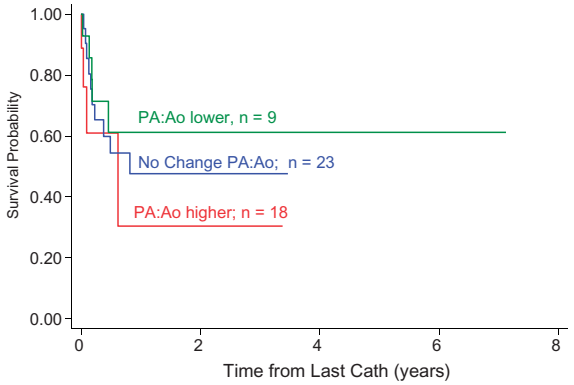

Fig. 3. The change in PA:Ao between the initial and last heart catheterization relative to survival. PA:Ao lower indicates a ≥ 1 level decrease in PA:Ao (e.g. > 0.5, < 1.0 at initial cath but ≤ 0.5 at last cath); analogously PA:Ao higher indicates a ≥ 1 level increase in PA:Ao. n = the number of patients in each category. Although there is a trend for a decrease in PA:Ao to be associated with increased survival, this trend was not significant ($P = 0.45$).

Table 2. Pulmonary hemodynamics, right ventricular (RV) function, and survival.

Variables	n	%	Deaths (%)	*P*
PA:Ao, initial				0.05
≤0.5	17	22	2 (11.8)	
>0.5, <1.0	47	61	19 (40.4)	
≥1.0	13	17	7 (53.9)	
PA:Ao, last				<0.001
≤0.5	17	32	2 (11.8)	
>0.5, <1.0	31	57	16 (51.6)	
≥1.0	6	11	5 (83.3)	
RV systolic function, initial				0.15
Normal	44	42	14 (31.8)	
Mildly reduced	15	14	6 (40.0)	
Moderately reduced	8	8	3 (37.5)	
Severely reduced	7	7	5 (71.4)	
Not reported	31	30	13 (41.9)	
RV systolic function, last				<0.001
Normal	47	45	10 (21.3)	
Mildly reduced	10	10	4 (40.0)	
Moderately reduced	9	9	8 (88.9)	
Severely reduced	2	2	2 (100)	
Not reported	37	35	17 (46.0)	

P values from log-rank test.

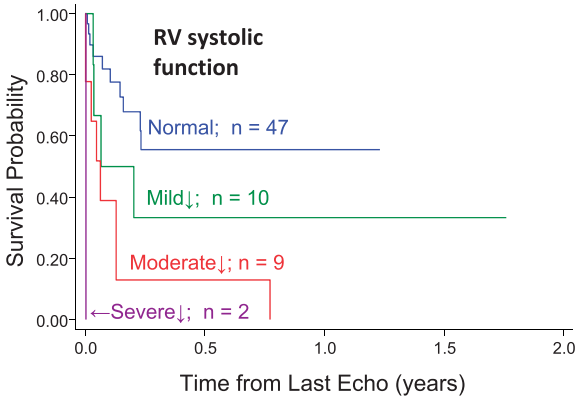

Fig. 4. Time to death tends to be shorten as RV systolic function worsens (last measured RV function); n = the number of patients at the time of the last echocardiogram; log-rank $P < 0.001$.

Table 3. Higher PA:Ao at first cardiac catheterization is associated with reduced RV systolic function by qualitative echocardiography.

	RV systolic function			
PA:Ao	Normal	Mildly reduced	Moderately reduced	Severely reduced
≤0.5	7	1	1	0
>0.5, <1.0	21	8	4	2
≥1.0	3	1	3	3

-0.13 ± 0.37, $P = 0.03$. At the initial catheterization, 14 of 27 patients (52%) had a ≥0.10 fall in PA:Ao, and in this sub-group the mean decrease in PA:Ao was -0.42 ± 0.38.

(6) Twenty patients had reactivity testing (six with 100% O_2 only) a total of 24 times. Thirteen patients (65%) met criteria for reactivity, although two subsequently lost this characteristic.

(7) Targeted PH medications (phosphodiesterase inhibitors, endothelin receptor antagonists, and prostanoids) were used in 32% of the patients. Sildenafil was the agent used in all but two cases (Table 1). Since only 13 patients (11 were on sildenafil) had optimal dosing of targeted therapy, and many other confounding variables impact hemodynamics and survival, we did not attempt to relate the use of targeted therapy to PA:Ao or survival.

Discussion

To our knowledge, this is the only reported data regarding both pulmonary hemodynamics and RV systolic function, including correlating RV function with PA:Ao, for patients with PVS. Poor RV systolic function has been shown to be associated with reduced survival and adverse events with other causes of elevated RV pressure.[10–12] Our experience is consistent with this and suggests that qualitative estimates of RV function by 2D echocardiography (as contrasted with quantitative analysis) may be useful as a predictor of survival with PVS (Table 2 and Fig. 3).

We also found that the magnitude of PH is negatively correlated with length of survival (Table 2 and Figs. 2 and 3). With idiopathic PH, PAP has not been found to associate with survival, or—paradoxically—lower PAP correlates with longer survival,[13–15] although higher PAP correlated with decreased survival with mitral stenosis in one report,[16] and another suggests that the balance of PA to systemic pressure may be important.[8] Of particular interest with respect to our patients, PA:Ao ≥ 0.5 at the initial interventional cardiac catheterization at BCH was predictive of mortality. In fact, those with normal or at most mildly elevated PAP early on had distinctly better survival prospects than those with significant PH, indicating that for this relatively small subset outcomes can be much better than is generally assumed for PVS.

This study does not establish whether PH and/or RV dysfunction are the reason(s) for reduced survival or surrogates for something else (e.g. severity of PVS), but it does suggest that that these variables may be useful, if imperfect, prognosticators for survival in this disease. But it is important to appreciate that mortality in PVS can occur without RV dysfunction, that PA pressure can fall with therapy, and that patients with a well-adapted RV may do well despite severe PH (point 4 in "Results"). Thus, our data do not suggest that PA pressure or RV function should be used as sole

outcome prognosticators, especially those measured at initial evaluation, since in some patients these will improve.

There were no complications related to acute vasodilator testing. Both vasodilator gases (iNO, O2) and PV dilation acutely reduced the PA:Ao in over half of the patients. Since patients with mitral stenosis show an acute fall in PAP with reduction in left atrial pressure and iNO,[17] and some patients with Group 1 PH are "reactive,"[10] this is not surprising. Given the small number of patients who had reactivity testing, and multiple confounding factors, we did not attempt to relate reactivity to survival or other outcome endpoints.

Our observations leave unanswered a fundamental question: is the PH solely a reflection of pulmonary venous hypertension, and increased flow through what vessels remain open in a restricted pulmonary vascular bed, or do some or all of these patients have a pan-vasculopathy? In other words, is the pathological remodeling in small PAs observed with PVS[18,19] simply a reaction to pulmonary venous hypertension, or a primary process? The reduction of PA:Ao with PV balloon dilation suggests that downstream obstruction plays a role, although this does not certify that pulmonary venous obstruction is the sole stimulus. We do know that, in general, Group 1 PAH is progressive, especially absent targeted therapy, and this may offer a clue with respect to the biology of PH with PVS: therapeutic relief of PVS, without using targeted therapy, accompanied by reversal of PH suggests that small PA remodeling is more likely due to pulmonary venous hypertension than a primary process.

Whether targeted PH therapy is useful in this setting remains an open question as well. Targeted therapy is generally thought to not be indicated for PH due to pulmonary venous hypertension or lung disease, although the effect of these drugs in these contexts is still not definitively established.[10,17] Although it would be clearly desirable to reduce PAP, several concerns need to be considered before broadly utilizing targeted therapy: unknown efficacy of targeted therapy in decreasing PVR in this setting; possibly unfavorable effects on ventilation-perfusion matching and/or lung water; questionable utility if the PVS proves relentless despite therapy. Also relevant to future clinical studies, phosphodiesterase inhibitors, endothelin receptor antagonists, and prostanoids may affect vascular remodeling and thus make it hard to determine the effect of other therapies on pathological remodeling in PVS. These drugs should therefore be carefully designed into (or out of) future studies to facilitate interpreting the information obtained.

Limitations

First, although the data presented are from patients in a well-defined cohort, the clinically driven tests were variable in timing and the number performed. Also, patients died or were lost to follow-up at variable intervals, and in some cases cardiac catheterization or echocardiogram reports lacked information needed. Data were therefore analyzed from multiple sub-groups of patients rather than reflecting a longitudinal look at all patients. Overall patient characteristics given on Table 1 therefore do not necessarily reflect the average characteristics of each of the subgroups.

Second, we recognize that MRI or three-dimensional echocardiography may better assess RV systolic performance than subjectively-graded 2D echocardiography,[20,21] but few of our patients had advanced imaging. That said, Altman et al. found qualitative assessment of RV function to predict survival acceptably well in neonates with a single ventricle,[22] and our data suggest that qualitative echocardiographic assessment of RV function may be sufficient to predict survival in PVS patients at our center, although this may not be true in all centers.

Conclusions

PH is a major component of our PVS patients' phenotype, with almost 80% of our patients having PH at initial catheterization, and elevated PA:Ao being associated with reduced survival. RV function is reduced in many and is also associated with impaired survival. The RV dysfunction is associated with higher PA:Ao, suggesting that dysfunction is mostly related to increased afterload rather than other factor(s). RV function, as assessed by 2D echocardiography, and PA:Ao appear to be predictors of survival and may prove useful in that regard. Given the important impact of PH on survival in this disease, clinical studies of medications or other treatments should include measures of PAP and RV function as important variables of interest, and careful study design will take into account the fact that targeted PH therapy may affect remodeling of both small pulmonary arteries and large PVs.

Acknowledgments

The authors thank Lynne Patkin, MBA, for her expert assistance in preparing this manuscript.

Declaration of conflicting interests

The author(s) declare that there is no conflict of interest.

Funding

This work was supported by a grant from Matthew's Hearts of Hope (Sherman, CT, USA).

ORCID iD

Kristofer Andren http://orcid.org/0000-0002-5090-3086

References

1. Bernstein J, Nolke AC and Reed JO. Extrapulmonic stenosis of the pulmonary veins. *Circulation* 1959; 19: 891–897.
2. Sherman FE, Stengel WF and Bauersfeld SR. Congenital stenosis of pulmonary veins at their atrial junctions. *Am Heart J* 1958; 56: 908–919.
3. Driscoll DJ, Hesslein PS and Mullins CE. Congenital stenosis of individual pulmonary veins: clinical spectrum and

unsuccessful treatment by transvenous balloon dilation. *Am J Cardiol* 1982; 49: 1767–1772.
4. Bini RM, Cleveland DC, Ceballos R, et al. Congenital pulmonary vein stenosis. *Am J Cardiol* 1984; 54: 369–375.
5. Seale AN, Webber SA, Uemura H, et al. Pulmonary vein stenosis: the UK, Ireland and Sweden collaborative study. *Heart* 2009; 95: 1944–1949.
6. Gowda S, Bhat D, Feng Z, et al. Pulmonary vein stenosis with Down syndrome: a rare and frequently fatal cause of pulmonary hypertension in infants and children. *Congenit Heart Dis* 2014; 9: E90–97.
7. Laux D, Rocchisani MA, Boudjemline Y, et al. Pulmonary hypertension in the preterm infant with chronic lung disease can be caused by pulmonary vein stenosis: a must-know entity. *Pediatr Cardiol* 2016; 37: 313–321.
8. Zhang HD, Lv ZC, Wang LT, et al. Prognostic significance of reduced blood pressure response to exercise in pediatric pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2017; 196: 1478–1481.
9. Seale AN and Daubeney PEF. Pulmonary vein stenosis–novel strategies for a challenging and resistant condition? *J Thorac Cardiovasc Surg* 2016; 151: 618–620.
10. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation* 2015; 132: 2037–2099.
11. Jone PN, Schafer M, Pan Z, et al. 3D echocardiographic evaluation of right ventricular function and strain: a prognostic study in paediatric pulmonary hypertension. *Eur Heart J Cardiovasc Imaging*. DOI: 10.1093/ehjci/jex205).
12. Moceri P, Duchateau N, Baudouy D, et al. Three-dimensional right-ventricular regional deformation and survival in pulmonary hypertension. *Eur Heart J Cardiovasc Imaging* 2018; 19: 450–458.
13. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.
14. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39: 589–596.
15. DuBrock HM, Goldberg DS, Sussman NL, et al. Predictors of waitlist mortality in portopulmonary hypertension. *Transplantation* 2017; 101: 1609–1615.
16. Nunes MCP, Tan TC, Elmariah S, et al. Net atrioventricular compliance is an independent predictor of cardiovascular death in mitral stenosis. *Heart* 2017; 103: 1891–1898.
17. Kulik TJ. Pulmonary hypertension caused by pulmonary venous hypertension. *Pulm Circ* 2014; 4: 581–595.
18. Sun CC, Doyle T and Ringel RE. Pulmonary vein stenosis. *Hum Pathol* 1995; 26: 880–886.
19. Pogoriler JE, Kulik TJ, Casey AM, et al. Lung pathology in pediatric pulmonary vein stenosis. *Pediatr Dev Pathol* 2016; 19: 219–229.
20. Margossian R, Schwartz ML, Prakash A, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging measurements of functional single ventricular volumes, mass, and ejection fraction (from the Pediatric Heart Network Fontan Cross-Sectional Study). *Am J Cardiol* 2009; 104: 419–428.
21. Bellsham-Revell HR, Tibby SM, Bell AJ, et al. Serial magnetic resonance imaging in hypoplastic left heart syndrome gives valuable insight into ventricular and vascular adaptation. *J Am Coll Cardiol* 2013; 61: 561–570.
22. Altmann K, Printz BF, Solowiejczky DE, et al. Two-dimensional echocardiographic assessment of right ventricular function as a predictor of outcome in hypoplastic left heart syndrome. *Am J Cardiol* 2000; 86: 964–968.