Received: 22 June 2017 | Revised: 17 November 2017 | Accepted: 19 December 2017

DOI: 10.1111/chd.12574

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Predictive value of presuperior cavopulmonary anastomosis cardiac catheterization at increased altitude

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Funding information
None

Abstract

Objective: Infants with single ventricle physiology typically undergo cardiac catheterization prior to superior cavopulmonary anastomosis (SCPA) to assess operative suitability. Predictors of poor outcome at sea level include elevated pulmonary artery pressure (mPAP), indexed pulmonary vascular resistance (PVRi), age <3 months, significant atrioventricular valve regurgitation, among others. Increased altitude has vasoconstrictive effects on the pulmonary vasculature, which may affect pre-SCPA hemodynamics and outcomes. The goal of this study was to determine the predictive value of pre-SCPA catheterization data with regard to reaching Fontan palliation at altitude.

Design: A retrospective review revealed 150 patients who underwent pre-SCPA catheterization over a 10-year period. Subjects were grouped by progression to Fontan vs aborted palliation, heart transplant or death. Statistics included *t*-tests, logistic regression and receiver operator characteristic (ROC) curve analysis.

Results: Independent predictors of failure to achieve Fontan operation at increased altitude include decreased ventricular function, increased mPAP, increased PVRi, and prolonged hospitalization, after adjusting for ventricular morphology and sex.

Conclusions: Our data indicate that decreased ventricular function most strongly predicts failure to reach Fontan palliation. Additionally, mPAP and PVRi play an important role in determining outcomes at increased altitude. Prolonged hospitalization is likely a marker of increased medical complexity or more problematic physiology.

KEYWORDS
cardiac catheterization, Fontan, survival

1 | INTRODUCTION

Infants with single ventricle (SV) physiology convetionally undergo cardiac catheterization prior to superior cavopulmonary anastomosis (SCPA) to assess operative suitability.[1] This approach has not only been used to risk stratify patients prior to surgery but also provides an opportunity to intervene and optimize hemodynamics; for example, pre-SCPA catheterization allows for aortic arch angioplasty in the setting of recurrent coarctation of the neo-aorta following Norwood-type arch reconstruction. The consequence of incorrectly recommending that an infant proceed with SCPA based on pre-SCPA diagnostic studies may be catastrophic, necessitating reversion to systemic to pulmonary arterial shunt and entailing significant morbidity or mortality. At sea level, risk factors for poor outcomes after SCPA have been identified, and include a dominant right ventricle, heterotaxy syndrome, anomalous pulmonary venous drainage, atrioventricular valve insufficiency, age <3 months at SCPA, prolonged hospitalization following Norwood operation, prolonged cardiopulmonary bypass time, low weight-for-age *z*-score, elevated mean transpulmonary gradient (TPG), and indexed pulmonary vascular resistance (PVRi).[2–9] Pre-SCPA risk factors at increased altitude have been inadequately studied, and may improve understanding of pre-SCPA physiology and provide broadly applicable insights.

Few studies have assessed the feasibility of single ventricle palliation at increased altitude, and the predictive value of data obtained at pre-

SCPA cardiac catheterization has not been evaluated. Previous work at our center (Denver, CO, altitude 1604 m) includes a review of pre-SCPA hemodynamic data, revealing associations between invasively derived hemodynamic data and failed Fontan operation: mPAP >15 mm Hg, TPG >8 mm Hg, PVRi >2.5WU[10]; however, the predictive value of pre-SCPA hemodynamics was not addressed. Subsequently, a multicenter study evaluating pre-SCPA hemodynamic data at institutions at three different altitudes (Denver at 1604 m, Edmonton at 668m and Toronto at 103m above sea level) did not show an association between increased altitude and elevated pulmonary vascular resistance (PVR) or adverse outcomes. Other investigators have shown impaired exercise capacity[11,12] and worse survival[13] in patients with palliated single ventricle physiology at increased altitude. These incongruous data raise important questions as to the utility of pre-SCPA cardiac catheterization at increased altitude; more specifically, what elements of the preoperative evaluation are independent predictors of adverse outcomes?

The aim of this study was to: (1) retrospectively evaluate a cohort of infants undergoing SCPA at increased altitude, and (2) determine the predictive value of data obtained during the pre-SCPA assessment with regard to failure to achieve Fontan completion. Our hypothesis is that pulmonary hemodynamics and pulmonary artery morphology are crucial determinants of the ability to achieve Fontan palliation in this setting, perhaps even more so than at sea level.

2 | METHODS

2.1 | Study design

A retrospective case-control study was undertaken. Subjects were grouped by the primary outcome: death, heart transplant or aborted palliation vs Fontan or those in NYHA class I awaiting Fontan operation. Potential relationships between suspected risk factors for adverse outcomes were made between these groups.

2.2 | Study population

A retrospective review of the medical records of infants undergoing SCPA at Children's Hospital Colorado between January 2003 and December 2011 was performed. Institutional review board approval was obtained. The surgical database was utilized as a means of identifying patients. Subjects were excluded if they underwent SCPA as part of a "one-and-a-half" ventricle palliation or transferred care to another cardiologist immediately after SCPA. As our institution is a referral center for many practices in rural parts of the mountain west, it is not uncommon for area pediatric cardiologists in adjacent states to send patients to our center for an operation and subsequently follow them independently thereafter.

2.3 | Predictor variables

Demographic and anthropometric data were abstracted. Data pertaining to the subject's initial hospitalization were reviewed, including the need for neonatal intervention, surgical shunt type, postoperative neonatal feeding modality, and length of initial hospital stay. Prior to SCPA, patients at our institution undergo routine echocardiography and cardiac catheterization. The need for home oxygen and pulmonary vasodilators at the time of pre-SCPA catheterization history and physical were noted. Echocardiographic data was reviewed for both cardiac morphology and function, including subjective evaluation of ventricular performance and atrioventricular valve insufficiency. Due to the significant proportion of subjects cared for primarily by referring cardiologists in the mountain west, a proportion of the pre-SCPA echo reports were done prior to transfer and unavailable for review; similarly, legacy reports predating the initiation of our electronic medical record were at times missing. When performed at our center, proximal pulmonary artery diameter was routinely reported on echocardiogram reports, and this data was abstracted. Pre-SCPA hemodynamic data were also reviewed, including saturations, pressures, pulmonary and systemic blood flow and resistances, and anatomic data based on angiograms. As access to the pulmonary arteries is limited in infants with shunt-dependent pulmonary blood flow, pulmonary venous wedge pressures were used as a surrogate for pulmonary artery pressures. For the purposes of evaluating pulmonary arterial size, the minimum diameter of the proximal pulmonary artery both rightward and leftward of the surgical shunt was remeasured manually by an investigator (MD) using clinically available medical image viewing software (AGFA Healthcare Cardiovascular Review Station version 2.14.03, Mortsel, Belgium). Peri-operative data were also reviewed, including subject characteristics at the time of SCPA, cardiopulmonary bypass (CBP) time, cross-clamp time (XCT), and the need for deep hypothermic circulatory arrest (DHCA). SCPA type was recorded, along with any ancillary procedures, such as pulmonary arterioplasty, and so forth. The post-SCPA hospital course was reviewed, and ventilation time, ICU stay, and total hospital stay were recorded.

2.4 | Statistical methods

Of 180 patients undergoing pre-SCPA catheterization, 150 had valid outcomes (Fontan, awaiting Fontan, aborted Fontan, Died, or Transplanted) and were therefore eligible for inclusion in the study. Patient demographics, pre-SCPA echocardiogram measures, pre-SCPA catheterization measures, and peri-operative factors were descriptively assessed by treatment success/failure using means and 95% confidence intervals for continuous variables and counts and percentages for categorical variables. To assess initial differences by outcome, *t*-tests were used for continuous variables and chi-square tests, or Fisher's exact test with expected cell counts less than 5, were used for categorical variables.

The primary analysis used simple logistic regression to assess the association of key demographic, echo, and catheter measurements with treatment failure. Logistic regression models of treatment outcome on pulmonary artery diameters were also assessed using ROC curves, AUC, sensitivity, and specificity. A significance level of 0.05 was used for hypothesis tests. Data cleaning and analysis were conducted using R version 3.3.2 (2016-10-31) (http://www.R-project.org). ROC curves, associated statistics, and cut point identification were conducted using the R package *pROC*.[14] Figures were created with the R packages *qwraps2* (https://CRAN.R-project.org/package=qwraps2) and *ggplot2* (http://had.co.nz/ggplot2/book).

TABLE 1 Patient demographics by outcome

	Total (N = 150) Mean (CI) or N (%)	Treatment success: Fontan or awaiting Fontan (N = 117) Mean (CI) or N (%)	Treatment failure: aborted palliation, died, transplanted (N = 33) Mean (CI) or N (%)	*P* value
Gestational age (wks)	38.13 (37.75, 38.51)	38.20 (37.80, 38.60)	37.90 (36.94, 38.86)	.5739
Birth weight (kg)	3.02 (2.91, 3.14)	3.08 (2.96, 3.20)	2.86 (2.58, 3.13)	.1614
Gender (% male)	84/150 (56.00%)	66/117 (56.41%)	18/33 (54.55%)	1.0000
Heterotaxy	20/149 (13.42%)	14/116 (12.07%)	6/33 (18.18%)	.3893
Genetic syndrome	9/145 (6.21%)	7/114 (6.14%)	2/31 (6.45%)	1.0000
Dominant ventricle				**.0004**
HLHS	49/150 (32.67%)	31/117 (26.50%)	18/33 (54.55%)	
Single RV	24/150 (16.00%)	16/117 (13.68%)	8/33 (24.24%)	
Single LV	77/150 (51.33%)	70/117 (59.83%)	7/33 (21.21%)	
Norwood-type arch reconstruction	62/150 (41.33%)	42/117 (35.90%)	20/33 (60.61%)	**.0190**
Shunt type				**.0211**
No shunt	39/150 (26.00%)	35/117 (29.91%)	4/33 (12.12%)	
Blalock-Taussig	54/150 (36.00%)	45/117 (38.46%)	9/33 (27.27%)	
Sano	44/150 (29.33%)	28/117 (23.93%)	16/33 (48.48%)	
Other	13/150 (8.67%)	9/117 (7.69%)	4/33 (12.12%)	
Stage 1 LOS (days)	38.24 (32.68, 43.81)	33.48 (27.27, 39.70)	54.39 (43.83, 64.95)	**.0016**
Supplemental oxygen at pre-SCPA catheterization	55/150 (32%)	32/117 (27.3%)	16/32 (50%)	**.015**
Pulmonary vasodilator at pre-SCPA catheterization	1/150 (0.6%)	1/117 (0.8%)	0/32 (0%)	.6

3 | RESULTS

3.1 | Study participants

Of the 180 patients who underwent SCPA during the specified time-period, 150 met inclusion criteria for analysis. Of the patients who were excluded, 20 were not seen again at our institution after discharge and 10 underwent a variation of a one-and-a-half ventricle palliation. Baseline characteristics of the 20 patients who were operated on and followed elsewhere were compared to the rest of the subjects, and there were no significant differences.

3.2 | Sample characteristics

Sample characteristics are presented in Table 1, with 117 patients achieving or awaiting Fontan palliation, and 33 patients having died, failed palliation, or had a heart transplant. There was no significant difference in median gestational age (GA), birth weight, gender, and the frequency of heterotaxy or other clinically evident genetic syndrome. The adverse outcome group had a higher incidence of dominant right ventricle ($P < .001$), Norwood-type arch reconstruction ($P = .019$), and Sano shunt ($P = .021$). The adverse outcome group also had a longer length of stay during their initial hospitalization ($P = .002$).

Subjects in the treatment failure group experienced a variety of adverse outcomes. Heart transplant was performed in 9 cases. Twenty-one subjects in this cohort died, with the cause of death related to infectious complications in 4 cases, sequelae of plastic bronchitis in 3 cases, inoperable structural heart disease in 4 cases, heart transplant graft rejection in 2 cases and uncertain in 8 cases.

3.3 | Echocardiographic data

Pre-SCPA echocardiographic data are presented in Table 2. Subjects with more severe AV valve insufficiency appeared more frequently in the adverse outcome group ($P = .04$). More significant ventricular dysfunction was present in the subjects who failed to achieve Fontan completion ($P = .005$). There were very few subjects with significant semilunar valve insufficiency, and no difference between outcome groups.

3.4 | Invasive hemodynamic data

Data obtained at pre-SCPA cardiac catheterization are shown in Table 3. Subjects in the adverse outcome group had lower mixed venous saturation ($P = .032$). There was no difference in mean arterial pressure, or mean PVRi. Of note, the minimum diameter of the pulmonary artery both rightward and leftward of the shunt was significantly smaller in the adverse outcome group ($P = .013$ and .007 in the neo-left pulmonary artery (LPA) and right pulmonary artery (RPA), respectively).

3.5 | Peri-operative data

As shown in Table 4, there were no differences in age or weight at SCPA between the outcome groups. Utilization of enteral tube feedings at the time of SCPA was more common in the adverse outcome group, with borderline statistical significance ($P = .05$). Duration of CPB and XCT and the frequency of DHCA utilization were

TABLE 2 Pre–superior cavopulmonary anastomosis echocardiogram

	Total (N = 150) Mean (CI) or N (%)	Treatment success: Fontan or awaiting Fontan (N = 117) Mean (CI) or N (%)	Treatment failure: aborted palliation, died, transplanted (N = 33) Mean (CI) or N (%)	*P* value
AV valve insufficiency				**.0401**
None/trace	66/102 (64.71%)	55/79 (69.62%)	11/23 (47.83%)	
Mild	25/102 (24.51%)	19/79 (24.05%)	6/23 (26.09%)	
Moderate	7/102 (6.86%)	3/79 (3.80%)	4/23 (17.39%)	
Severe	4/102 (3.92%)	2/79 (2.53%)	2/23 (8.70%)	
Ventricular function				**.0051**
Normal	97/106 (91.51%)	79/82 (96.34%)	18/24 (75.00%)	
Mildly depressed	6/106 (5.66%)	2/82 (2.44%)	4/24 (16.67%)	
Moderately depressed	1/106 (0.94%)	0/82 (0.00%)	1/24 (4.17%)	
Severely depressed	2/106 (1.89%)	1/82 (1.22%)	1/24 (4.17%)	
Semi-lunar valve insufficiency				**.3951**
None/trace	102/104 (98.08%)	80/81 (98.77%)	22/23 (95.65%)	
Mild	1/104 (0.96%)	0/81 (0.00%)	1/23 (4.35%)	
Moderate	1/104 (0.96%)	1/81 (1.23%)	0/23 (0.00%)	
Severe	0/104 (0.00%)	0/81 (0.00%)	0/23 (0.00%)	

similar. Many subjects underwent right-sided bidirectional Glenn (BDG), with no difference in the frequency of bilateral or left-sided BDG between the outcome groups. A history of atrioventricular valvuloplasty, pulmonary arterioplasty, and aortic arch intervention during SCPA was not associated with an adverse outcome. Ventilation time and ICU stay were almost identical, but the total post-SCPA hospital stay was longer in the group failing to reach Fontan completion ($P = .005$).

TABLE 3 Pre-superior cavopulmonary anastomosis cardiac catheterizations

	Total (N = 150) Mean (CI) or N (%)	Treatment success: Fontan or awaiting Fontan (N = 117) Mean (CI) or N (%)	Treatment failure: aborted palliation, died, transplanted (N = 33) Mean (CI) or N (%)	*P* value
Body surface area (m^2)	0.31 (0.29, 0.32)	0.31 (0.30, 0.32)	0.29 (0.27, 0.31)	.0553
Hemoglobin (g/dL)	14.14 (13.76, 14.52)	14.08 (13.70, 14.47)	14.37 (13.28, 15.46)	.6288
Arterial saturation (%)	71.99 (70.52, 73.46)	72.61 (70.92, 74.30)	69.54 (66.85, 72.23)	.0652
Mixed venous saturation (%)	49.84 (48.33, 51.35)	50.73 (49.09, 52.37)	46.38 (42.92, 49.83)	.0321
Mean atrial pressure (mm Hg)	6.06 (5.64, 6.48)	5.90 (5.47, 6.33)	6.67 (5.45, 7.88)	.2545
Ventricular EDP (mm Hg)	6.86 (6.35, 7.37)	6.80 (6.25, 7.36)	7.08 (5.85, 8.32)	.6872
Mean arterial pressure (mm Hg)	55.94 (53.99, 57.89)	56.52 (54.42, 58.62)	53.67 (48.70, 58.63)	.3070
Peak-to-peak aortic arch gradient (mm Hg)	4.79 (3.14, 6.45)	4.33 (2.45, 6.21)	6.54 (3.10, 9.99)	.2763
Mean PA pressure (mm Hg)	14.83 (14.05, 15.61)	14.47 (13.67, 15.26)	16.22 (14.08, 18.36)	.1439
Transpulmonary gradient (mm Hg)	8.87 (8.15, 9.59)	8.64 (7.89, 9.40)	9.74 (7.83, 11.65)	.3043
Minimum RPA diameter (mm)	5.99 (5.57, 6.42)	6.26 (5.77, 6.75)	5.00 (4.26, 5.74)	**.0077**
Diffusely hypoplastic RPA	9/117 (7.69%)	7/93 (7.53%)	2/24 (8.33%)	1.0000
Minimum LPA diameter (mm)	6.16 (5.72, 6.59)	6.43 (5.95, 6.91)	5.13 (4.27, 5.98)	**.0132**
Diffusely hypoplastic LPA (mm)	9/118 (7.63%)	7/94 (7.45%)	2/24 (8.33%)	1.0000
Indexed pulmonary blood flow ($L/min/m^2$)	4.12 (3.84, 4.40)	4.21 (3.88, 4.53)	3.82 (3.24, 4.39)	.2516
Indexed systemic blood flow ($L/min/m^2$)	4.59 (4.25, 4.93)	4.71 (4.30, 5.11)	4.15 (3.60, 4.70)	.1146
Ratio of pulmonary to systemic blood flow	1.00 (0.92, 1.08)	1.01 (0.92, 1.11)	0.97 (0.84, 1.10)	.5879
Indexed pulmonary vascular resistance (WU/m^2)	2.10 (1.91, 2.29)	2.01 (1.82, 2.19)	2.46 (1.89, 3.02)	**.1525**
Indexed systemic vascular resistance (WU/m^2)	12.71 (11.72, 13.69)	12.73 (11.60, 13.85)	12.63 (10.54, 14.73)	**.0132**

TABLE 4 Peri-operative factors

	Total (N = 150) Mean (CI) or N (%)	Treatment success: Fontan or awaiting Fontan (N = 117) Mean (CI) or N (%)	Treatment failure: aborted palliation, died, transplanted (N = 33) Mean (CI) or N (%)	*P* value
Age at SCPA (days)	221.83 (184.51, 259.14)	193.07 (175.85, 210.29)	323.79 (168.69, 478.89)	.1102
Weight at SCPA (kg) (*P* =)	6.23 (5.94, 6.52)	6.12 (5.87, 6.37)	6.60 (5.63, 7.58)	.3546
Feeding modality at the time of SCPA				**.0502**
Oral	92/150 (61.33%)	79/117 (67.52%)	13/33 (39.39%)	
Any NG	32/150 (21.33%)	22/117 (18.80%)	10/33 (30.30%)	
Any G-tube	20/150 (13.33%)	14/117 (11.97%)	6/33 (18.18%)	
Cardiopulmonary bypass time (min)	97.54 (88.97, 106.10)	92.68 (84.55, 100.81)	114.61 (89.04, 140.17)	.1173
Cross-clamp time (min)	18.38 (14.35, 22.41)	17.44 (13.31, 21.58)	21.70 (10.65, 32.74)	.4836
Deep hypothermic circulatory arrest	28/149 (18.79%)	20/116 (17.24%)	8/33 (24.24%)	.4483
SCPA type				.6395
Right-sided bidirectional Glenn	128/150 (85.33%)	101/117 (86.32%)	27/33 (81.82%)	
Bilateral bidirectional Glenn	11/150 (7.33%)	8/117 (6.84%)	3/33 (9.09%)	
Left-sided bidirectional Glenn	6/150 (4.00%)	5/117 (4.27%)	1/33 (3.03%)	
Other	5/150 (3.33%)	3/117 (2.56%)	2/33 (6.06%)	
Atrioventricular valvuloplasty	6/147 (4.08%)	3/115 (2.61%)	3/32 (9.38%)	.1175
Pulmonary arterioplasty	66/148 (44.59%)	49/116 (42.24%)	17/32 (53.12%)	.3177
Aortic arch intervention	12/148 (8.11%)	9/116 (7.76%)	3/32 (9.38%)	.7226
Ventilation time (hours)	2.36 (0.71, 4.01)	1.67 (0.25, 3.09)	5.35 (−0.90, 11.60)	.2706
ICU stay (days)	5.00 (3.15, 6.85)	4.68 (2.52, 6.84)	6.56 (3.80, 9.31)	.3003
Hospital stay (days)	13.34 (10.09, 16.60)	9.62 (7.21, 12.02)	26.97 (15.69, 38.25)	**.0058**

3.6 | Logistic regression

Univariate logistic regression was performed, presented in Table 5. There were significant associations between treatment failure and stage 1 LOS, as well as other variables including: mixed venous saturation, left and right pulmonary artery diameter, ventricular morphology, Norwood-type arch reconstruction, shunt type and ventricular function by echocardiogram. Multivariable logistic regression is presented in Table 6. After adjusting for ventricular morphology and sex, independent predictors of treatment failure included ventricular function, stage 1 LOS, post-SCPA hospital stay, mPAP and PVRi.

3.7 | Receiver operator characteristic curves

Area under the curve (AUC) and 95% confidence intervals for predictor variables are presented in Table 7. Stage 1 LOS and post-SCPA hospital stay had the highest AUC, 0.785 and 0.759, respectively.

4 | DISCUSSION

We showed that the independent predictors of failure to achieve Fontan operation at increased altitude include decreased ventricular function, increased mPAP, increased PVRi, and prolonged hospitalization, after adjusting for ventricular morphology and sex. Of these predictors, decreased ventricular function was most predictive of treatment failure, with an odds ratio of 7.2 and an adjusted AUC of 0.750 on ROC analysis. Prolonged hospitalization, both at the time of stage 1 palliation and after SCPA were also predictors of treatment failure; like the need for supplemental oxygen, this appears to be a surrogate for higher medical complexity and perhaps borderline single ventricle postoperative hemodynamics in some cases.

Our findings are similar to the established risk factors noted in the literature,[2–9] which notably include increased mPAP and PVRi. Univariate regression also revealed associations between treatment failure

TABLE 5 Univariate logistic regression

Covariate	OR	CI lower	CI upper	*P* value
Stage 1 LOS (days)	1.02	1.01	1.04	.0074 *
Arterial saturation (%)	0.96	0.91	1.01	.1243
Mixed venous saturation (%)	0.94	0.89	0.99	.0290 *
Peak-to-peak aortic arch gradient (mm Hg)	1.02	0.98	1.07	.2951
Minimum LPA diameter (mm)	0.74	0.56	0.93	.0176 *
Minimum RPA diameter (mm)	0.73	0.55	0.93	.0206 *
Post-SCPA hospital stay (days)	1.04	1.02	1.07	.0015 *
Mean PA pressure (mm Hg)	1.10	0.99	1.23	.0780
Indexed PVR ($WU*m^2$)	1.53	0.96	2.53	.0745
Transpulmonary gradient (mm Hg)	1.07	0.95	1.20	.2279

TABLE 6 Multivariable logistic regression

Covariate	OR	CI lower	CI upper	*P* value	AUC (95% CI)
Depressed ventricular systolic function	7.21	1.56	40.12	.0143 *	0.750 (0.641, 0.858)
Arterial saturation (%)	0.98	0.92	1.03	.4106	0.727 (0.620, 0.834)
Mixed venous saturation (%)	0.96	0.90	1.01	.1447	0.728 (0.612, 0.844)
Peak-to-peak aortic arch gradient (mm Hg)	1.01	0.96	1.06	.7355	0.720 (0.611, 0.830)
Minimum LPA diameter (mm)	0.79	0.59	1.01	.0808	0.752 (0.644, 0.860)
Minmum RPA diameter (mm)	0.80	0.59	1.04	.1111	0.732 (0.609, 0.855)
Post-SCPA hospital stay (days)	1.03	1.01	1.05	.0156 *	0.759 (0.658, 0.859)
Stage 1 LOS (days)	1.02	1.00	1.03	.0388 *	0.785 (0.690, 0.880)
Norwood-type aortic arch reconstruction	0.96	0.18	3.91	.9561	0.706 (0.601, 0.811)
Mean PA pressure (mm Hg)	1.13	1.01	1.29	.0423 *	0.741 (0.616, 0.866)
Indexed PVR (WU*m^2)	1.79	1.07	3.10	.0266 *	0.730 (0.597, 0.863)
Transpulmonary gradient (mm Hg)	1.13	0.99	1.29	.0799	0.739 (0.626, 0.852)

and proximal pulmonary artery size. The mechanism by which elevated mPAP or proximal pulmonary artery narrowing contributes to adverse outcomes in children undergoing single ventricle palliation may be related to decreased antegrade flow, elevated CVP, decreased ventricular preload, reduced cardiac output and resultant complications. As Fontan physiology is one of series circulations, with one ventricle required to move blood through two capillary beds, even minimal stenosis can lead to profound hemodynamic derangements over time. The clinical manifestation of systemic venous hypertension may include pleural effusions, plastic bronchitis, protein losing enteropathy, hepatic fibrosis, and related conditions.[15] The development of proximal pulmonary artery stenosis in patients with single ventricle physiology is multifactorial, and includes patient-specific factors related to pre-intervention cardiac morphology and surgical history. Residing at higher altitude therefore may result in altered growth of the pulmonary arteries starting early in development, perhaps even in utero. A study evaluating pulmonary artery characteristics in patients during single ventricle palliation would be of great interest and potential benefit, in search of strategies to maximize growth.

A previous study at our center by Malhotra et al. revealed higher mPAP and PVRi as risk factors for adverse outcomes.[10] We would like to address possible reasons for the disparate findings of these two studies; importantly, the study by Malhotra et al. did not address the predictive value of pre-SCPA data. The primary outcome for the study by Malhotra et al. was freedom from palliation failure, with the group achieving Fontan palliation subdivided into a "marginal" cohort and one with no functional impairment (NYHA class I). The group failing to achieve Fontan and the "marginal" cohort were not statistically different in nearly all comparisons between pre-SCPA hemodynamic variables. The present study combines all subjects who have had a Fontan operation and those in NYHA class I awaiting Fontan operation, which likely explains the different findings in these two studies. The differences may also be a result of shifting practice patterns over time, changes in surgical approach, and differences in postoperative care. More specifically, the present study includes subjects operated on between January 2003 and December 2011, while the study by Malhotra et al. includes those who underwent SCPA between January 1995 and March 2007.

TABLE 7 Adjusted area under the curve statistics

Covariate	AUC (95% CI)
Depressed ventricular systolic function	0.750 (0.641, 0.858)
Post-SCPA hospital stay (days)	0.759 (0.658, 0.859)
Stage 1 LOS (days)	0.785 (0.690, 0.880)
Mean PA pressure (mm Hg)	0.741 (0.616, 0.866)
Indexed PVR (WU*m^2)	0.730 (0.597, 0.863)

When compared with pre-SCPA hemodynamic data in the literature, our cohort's pulmonary hemodynamics appear similar to other groups at sea level. As demonstrated by Zhou et al., increased altitude may not be a strong determinant of pre-SCPA hemodynamics.[16] However, there are several complicating factors. First, the long-term effect of decreased ambient PaO_2 on Fontan hemodynamics has not been adequately assessed. Follow-up in the study by Zhou et al. ranged between 3 and 6 years at the different centers, leaving this issue unresolved. Anecdotally, we have observed several Fontan patients in our clinical practice with marginal single ventricle hemodynamics, struggling with comorbidities such as plastic bronchitis, who have had remarkable improvement in clinical status after a trial of living at sea level. Our colleagues in Salt Lake City, UT (elevation 1300 m), have made the converse observation, that patients with Fontan physiology who live at sea level and move to altitude may decompensate.[17] Similar to investigators in Australia and New Zealand,[18] albeit on a smaller scale, we plan to create a Fontan registry for patients cared for at our center for the purposes of long term follow-up and outcomes research at altitude. We hope that this will provide better understanding of the physiology of patients during single ventricle palliation, and provide information that can be applied to the care of all Fontan patients.

Given that preoperative cardiac catheterization carries a small but quantifiable risk, some centers have advocated for substituting a noninvasive imaging study such as cardiac magnetic resonance imaging (cMRI).[19] Brown et al. have shown that pre-SCPA cMRI is an acceptable alternative to cardiac catheterization certain patients, with no difference in clinical outcomes at a median age of 8.8 years. Our data support this assertion, but it is important to note that the impact of the lost opportunity to perform catheter-based interventions, such as coiling systemic to pulmonary arterial collaterals and dilating recurrent neo-aortic coarctation, has not been studied.

4.1 | Limitations

The retrospective nature of our data makes it susceptible to recall bias. Similarly, as this is a single center study, trends in outcome may be a reflection of internal practices. We have used "failure to achieve Fontal palliation" as a means of categorizing subjects, which has an element of subjectivity; the decision to forego the next step of palliation due to unacceptable operative risk was made on an individual patient basis by the primary cardiologist and surgeon.

Our measurements of pulmonary artery diameter were made on a single projection pulmonary arteriogram, when it is clear based on cross-sectional imaging that the pulmonary arteries are often oval-shaped. The fact that proximal pulmonary artery diameter is still associated with adverse outcomes suggests to us that this association is robust, given its statistical significance in the setting of suboptimal conditions. The Nakata index,[20] has been used other forms of congenital heart disease to characterize pulmonary artery size relative to body surface area. It was not calculated here, as biplane angiograms were not always available, and single plane measurements are not adequate for deriving cross-sectional area.

Survival analysis was complicated by the fact that several subjects who died were discharged on hospice care or died at other centers, making their date of death unknown; as such, Kaplan-Meier analysis was not attempted.

4.2 | Conclusions

The results of this study indicate that pre-SCPA cardiac catheterization hemodynamic data at altitude provide valuable prognostic data with regard to PVRi and mPAP, but depressed ventricular function was the strongest independent predictor of treatment failure. Other risk factors for adverse outcome are similar to previously published reports, and are likely surrogates for more problematic single ventricle physiology.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTIONS

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How to cite this article: Di Maria MV, Mulvahill M, Jaggers J, Ivy DD, Younoszai AK. Predictive value of presuperior cavopulmonary anastomosis cardiac catheterization at increased altitude. *Congenital Heart Disease*. 2018;13:311–318. https://doi.org/10.1111/chd.12574