World Journal for Pediatric and Congenital Heart Surgery
2023, Vol. 14(6) 691-698

DOI: 10.1177/21501351231185111
journals.sagepub.com/home/pch

Protein-Losing Enteropathy and Plastic Bronchitis Following the Total Cavopulmonary Connections

Veronika Hammer, MS[1,2,‡], Thibault Schaeffer, MD[1,2,‡], Helena Staehler, MS[1,2], Paul Philipp Heinisch, MD, PhD[1,2], Melchior Burri, MD[3], Nicole Piber, MD[3], Julia Lemmer, MD[4], Alfred Hager, MD, PhD[4], Peter Ewert, MD, PhD[4], Jürgen Hörer, MD, PhD[1,2], and Masamichi Ono, MD, PhD[1,2]

Abstract

Background: We aimed to evaluate incidence, outcomes, and predictors of protein-losing enteropathy (PLE) and plastic bronchitis (PB) in a cohort of total cavopulmonary connection (TCPC). **Methods:** We included 620 consecutive patients undergoing TCPC between 1994 and 2021. Prevalence and predictors for onset of PLE/PB were evaluated. Death and heart transplantation after onset of PLE/PB were examined. **Results:** A total of 41 patients presented with PLE/PB (31 with PLE, 15 with PB, and 5 developed both PLE and PB). Their median age at TCPC was 2.2 (interquartile ranges [IQRs], 1.7-3.7) years, and time period to onset for PLE was 2.6 (IQR: 1.0-6.6) years and for PB was 1.1 (IQR: 0.3-4.1) years after TCPC. Independent factors for developing PLE/PB were dominant right ventricle (RV, hazard ratio [HR], 2.243; 95% confidence interval [CI], 1.129-4.458, $P = .021$) and prolonged pleural effusion after TCPC (HR, 2.101; 95% CI, 1.090-4.049, $P = .027$). In PLE/PB population, freedom from death or transplantation after PLE/PB diagnosis at 5 and 10 years were 88.7% and 76.4%, respectively. Eleven surgical interventions were performed in 10 patients, comprising atrioventricular valve repairs (n = 4), Fontan pathway revisions (n = 2), pacemaker implantation (n = 2), secondary fenestration (n = 1), diaphragm plication (n = 1), and ventricular assist device implantation (n = 1). In nine patients, a recovery from PLE with the resolution of PLE symptoms and normal protein levels was achieved. Eight patients died and the remaining continued to have challenging protein loss. **Conclusions:** Protein-losing enteropathy and PB remain severe complications in the cohort of TCPC. Patients with dominant RV, and prolonged pleural effusions, were at risk for PLE/PB.

Keywords

Fontan, protein-losing enteropathy, plastic bronchitis, single ventricle, total cavopulmonary connection, ventricular assist device, heart transplantation

Submitted March 13, 2023; Accepted June 7, 2023.

Introduction

Although survival after the total cavopulmonary connection (TCPC) procedure is constantly improving, protein-losing enteropathy (PLE) and plastic bronchitis (PB) remain severe long-term complications.[1–9] Protein-losing enteropathy and PB occur in 3% to 18% of patients after the Fontan procedure and are two of the most important predictive factors of death and transplantation when they occur.[3,4] Survival after the onset of PLE and PB was reported in 46% to 88% of patients at 5 years.[3,5,6] The cause is uncertain; nevertheless, it is thought that an elevated central venous pressure and low cardiac output due to impaired ventricular preload characterized by the Fontan circulation play an important role.[5] This Fontan hemodynamic seems to result in uncontrolled loss of protein-rich lymphatic fluid, such as albumin, immunoglobulin, and clotting factors, into extra lymphatic compartments such as the gastrointestinal tract in PLE or bronchi in PB.[6] The protein loss that occurs leads to the clinical symptoms of peripheral edema, ascites, diarrhea, weight loss, and malabsorption. However, exact mechanisms are poorly understood and treatment strategies vary. Current treatments include medical therapy, aiming to reduce protein loss or improve cardiac

[1] Department of Congenital and Pediatric Heart Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany
[2] Division of Congenital and Pediatric Heart Surgery, University Hospital of Munich, Ludwig-Maximilians-Universität, Munich, Germany
[3] Department of Cardiovascular Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany
[4] Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich at the Technical University of Munich, Munich, Germany

[‡] Both authors contributed equally.

Corresponding Author:
Masamichi Ono, Department of Congenital and Pediatric Heart Surgery, German Heart Center Munich, Lazarettstraße 36, 80636, Munich, Germany.
Email: ono@dhm.mhn.de

Abbreviations

BCPS	bidirectional cavopulmonary shunt
DILV	double inlet left ventricle
HLHS	hypoplastic left heart syndrome
HR	hazard ratio
HTx	heart transplantation
IQR	interquartile range
PAB	pulmonary artery banding
PAPVC	partial anomalous pulmonary venous connection
PB	plastic bronchitis
PLE	protein-losing enteropathy
RV	right ventricle
TAPVC	total anomalous pulmonary venous connection
TCPC	total cavopulmonary connection
UVH	univentricular heart

function, as well as surgical therapies, such as atrioventricular valve repairs, Fontan pathway revisions, pacemaker implantation, or fenestration creation. In addition, there are various case reports where surgical decompression of the thoracic duct has been introduced as a possible treatment option for severe lymphatic failure, almost normalizing protein levels.[10–12] Heart transplantation (HTx) remains the ultimate treatment for those most severely affected by these complications.[13–15] However, it remains undetermined how to best treat patients who develop PLE or PB after TCPC and how to improve their expected survival.

Therefore, in this study, we intend to further define the incidence, outcomes, and risk factors of PLE and PB in a large cohort of patients after the TCPC, the current form of the Fontan procedure. In particular, we aim to identify (1) risk factors for PLE/PB after TCPC; (2) risk factors for death or transplant after PLE/PB; and (3) potential treatment strategies to minimize the clinical consequences of patients with PLE/PB.

Methods

Ethical Statement

This study was approved by the Institutional Review Board of the Technical University of Munich (approved number 2022-303-S-KH on June 27, 2022). Because of the retrospective nature of the study, the need for individual patient consent was waived.

Patients and Data Collection

This single-center retrospective cohort study included all patients who underwent a TCPC at the German Heart Center Munich from May 1994 to December 2021. Medical records included baseline morphology and demographics as well as preoperative, intraoperative, and postoperative data using electrical and paper chart reviews of each patient. The patients obtained outpatient follow-ups with pediatric cardiologists. The most current vital status and follow-up data were obtained from our institutional single ventricle database, which is regularly tracked. Follow-up times per patient were defined as the time from the TCPC to the time of the last visit. For patients who died, the endpoint of the survey was marked at the time of death.

Operative Techniques

The operative techniques for TCPC are described in previous reports.[16,17] Lateral tunnel TCPC was performed in 50 patients in the early era. In January 1999, extracardiac TCPC was introduced, and it has been our standard procedure since May 2002.[17] Fenestration was not routinely performed and was only used for high-risk patients.[16] Cavopulmonary support techniques with a modified cannulation technique are described in a previous report.[18]

Diagnosis of PLE and PB Following TCPC

Patients were regularly checked in the hospital and also in an outpatient clinic. PLE diagnosis was made by symptoms of edema without another identifiable cause, as defined by Rychik and colleagues' statement[2] from the American Heart Association, and also using an elevated a-1 antitrypsin clearance in a 24-h stool collection or an elevated a-1 antitrypsin level in a single stool sample together with the presence of serum hypoalbuminemia. The diagnosis of PB was made by expectoration of casts, bronchoscopy, and histologic examination. Patients with PLE and PB were pooled for analysis of their outcomes and the prediction of their occurrence. We examined two endpoints: death and cardiac transplantation.

Statistical Analysis

Categorical variables are presented as absolute numbers and percentages. A χ^2 test was used for categorical data. Continuous variables are expressed as medians with interquartile ranges (IQRs). An independent sample t test was used to compare normally distributed variables. The Mann-Whitney U test was used for variables that were not normally distributed. Levene's test was used to differentiate between normally and non-normally distributions. Freedom from PLE/PB and freedom from transplant survival was estimated using the Kaplan-Meier method, and differences between groups were determined using log-rank test. Competitive risk analysis for onset of PLE/PB and death/transplantation was performed. The results were reported as cumulative incidences. Risk factors for a failed Fontan completion were identified using univariate and multivariate Cox regression models. Data analysis was performed using SPSS version 28.0 for Windows (IBM) and R-statistical software (state package and cmprsk package).

Results

Patient Characteristics and Perioperative Data

During the study period, 620 patients underwent TCPC at our center. Patient characteristics are presented in Table 1.

Median age and median weight at TCPC were 2.3 (IQR: 1.8-3.4) years, and 12.0 (10.7-14.0) kg, respectively. Dominant right ventricle (RV) was observed in 329 (53%) and dominant left ventricle in 291 (47%) patients. The most frequent diagnosis was hypoplastic left heart syndrome (HLHS) in 172 patients, followed by univentricular heart (UVH) in 131, tricuspid atresia in 95, double inlet left ventricle (DILV) in 91, pulmonary atresia and intact ventricular septum in 32, congenitally corrected transposition of the great arteries in 29, and unbalanced atrioventricular septal defect in 25. Prior bidirectional cavopulmonary shunt was performed in 571 (92.1%) patients.

Incidence of PLE and PB

Among 620 patients, 10 patients were lost to follow-up after their hospital discharge. The median follow-up period was 5.9 (IQR: 1.2-13.1) years. We identified a total of 41 patients with PLE or PB (Table 1). Thirty-one had PLE only, 15 had PB only, and 5 had both. In these patients, the median age at TCPC was 2.2 years (IQR, 1.7-3.7 years), and the median time from TCPC to the onset of PLE/PB was 2.1 years (IQR, 1.0-6.3 years). The most commonly encountered diagnoses were HLHS in 17, UVH in 9, and DILV in 6, which accounted for the underlying pathology in more than half of the patients with PLE or PB (Table 1). Operative and postoperative variables are shown in Table 2.

There were 19 deaths in the Fontan population without PLE/PB (n = 579), whereas there were 10 deaths in the PLE/PB population (n = 41). There were four heart transplants (three non PLE/PB population and one PLE/PB population). No Fontan takedown was performed. There was a significant difference in survival between patients with and without PLE/PB (Supplementary Figure 1, $P = .002$, log-rank test). Competing risks plot is shown in Figure 1. The cumulative incidence of PLE/PB was 7.5% at 5 years, 11.7% at 10 years, and 12.2%

Table 1. Baseline Characteristics of the 620 Patients Who Underwent TCPC.[a]

Variable	Level	Total cases N = 620	No PLE or PB N = 579	PLE or PB N = 41	*P* value
Gender	Female	235 (37.9)	223 (38.5)	12 (29.3)	.35
	Male	385 (62.1)	356 (61.5)	29 (70.7)	
Dominant ventricle	Left	289 (46.6)	277 (47.8)	12 (29.3)	<.01
	Right	331 (53.4)	302 (52.2)	29 (70.7)	
Primary diagnosis	HLHS	172 (27.7)	155 (26.8)	17 (41.5)	<.01
	UVH	131 (21.1)	122 (21.1)	9 (22.0)	.65
	TA	95 (15.3)	92 (15.9)	3 (7.3)	.13
	DILV	91 (14.7)	85 (14.7)	6 (14.6)	.88
	PAIVS	32 (5.2)	31 (5.4)	1 (2.4)	.43
	ccTGA	29 (4.7)	29 (5.0)	0 (0.0)	.33
	UAVSD	25 (4.0)	23 (4.0)	2 (4.9)	.61
	Others	46 (7.4)	43 (7.4)	3 (7.3)	.90
Associated anomaly	TGA	208 (33.5)	193 (33.3)	15 (36.6)	.50
	DORV	81 (13.1)	75 (13.0)	6 (14.6)	.69
	CoA	79 (12.7)	74 (12.8)	5 (12.2)	.59
	TAPVC/PAPVC	42 (6.8)	36 (6.2)	6 (14.6)	.04
Isomerism	Yes	48 (7.7)	43 (7.4)	5 (12.2)	.25
Dextrocardia	Yes	56 (9.0)	53 (9.2)	3 (7.3)	.88
Initial palliation	Norwood/DKS	264 (42.6)	239 (41.3)	25 (61.0)	<.01
	AP shunt	185 (29.8)	176 (30.4)	9 (22.0)	.12
	PAB	90 (14.5)	82 (14.2)	8 (19.5)	.73
Prior BCPS	Yes	571 (92.1)	532 (91.9)	39 (95.1)	.06
Age at BCPS (months)	Median (IQR)	5.4 (3.6-10.5)	5.3 (3.6-10.5)	5.4 (4.0-9.5)	.16
Weight at BCPS (kg)	Median (IQR)	5.7 (4.8-7.1)	5.6 (4.7-7.1)	6.0 (4.7-7.4)	.36
Age at TCPC (years)	Median (IQR)	2.3 (1.8-3.4)	2.3 (1.8-3.4)	2.2 (1.7-3.7)	.07
Weight at TCPC (kg)	Median (IQR)	12 (11-14)	12 (11-14)	12 (11-14)	.10
TCPC type	LT	50 (8.1)	46 (7.9)	4 (9.8)	.19
	ECC	570 (91.9)	533 (92.1)	37 (90.2)	
Fenestration	Yes	46 (7.4)	41 (7.1)	5 (12.2)	.89
Prolonged pleural effusion	Yes	301 (48.5)	274 (47.3)	27 (65.9)	<.01
Chylothorax	Yes	131 (21.2)	116 (20.1)	15 (36.6)	<.01

Abbreviations: AP, aortopulmonary; BCPS, bidirectional cavopulmonary shunt; ccTGA, congenitally corrected transposition of the great arteries; CoA, coarctation of the aorta; DILV, double inlet left ventricle; DKS, Damus-Kaye-Stansel; DORV, double outlet right ventricle; ECC, extracardiac conduit; HLHS, hypoplastic left heart syndrome; LT, lateral tunnel; PA-IVS, pulmonary atresia-intact ventricular septum; PAB, pulmonary artery band; PB, plastic bronchitis; PLE, protein-losing enteropathy; TA, tricuspid atresia; TAPVC/PAPVC, total anomalous pulmonary venous connection/partial anomalous pulmonary venous connection; TCPC, total cavopulmonary connection; TGA, transposition of the great arteries; UAASD, unbalanced atrioventricular septal defect; UVH, univentricular heart.
[a]*P* value was calculated with Cox-regression model.

Table 2. Perioperative Variables.[a]

Variables	Total cases N = 620	No PLE or PB N = 579	PLE or PB N = 41	*P* value
Operative data				
Age at TCPC (years)	2.3 (1.8-3.4)	2.3 (1.8-3.4)	2.2 (1.7-3.7)	.07
Weight at TCPC (kg)	12 (11-14)	12 (11-14)	12 (11-14)	.10
Type of TCPC				
Intracardial	50 (8.1)	46 (7.9)	4 (9.8)	.19
Extracardiac	570 (91.9)	533 (92.1	37 (90.2)	
CPB time (min)	66 (47-102)	66 (47-101)	64 (54-116)	.76
Aortic cross clamp (AXC)	161 (26.0)	147 (25.4)	14 (34.1)	.68
AXC time (min)	46 (26-73)	46 (26-73)	42 (26-61)	.13
Concomitant procedure	164 (26.5)	149 (25.7)	15 (36.6)	.53
DKS	17 (2.7)	15 (2.6)	2 (4.9)	.67
AVV procedure	79 (12.7)	72 (12.4)	7 (17.1)	.46
PA reconstruction	59 (9.5)	52 (9.0)	7 (17.1)	.50
Atrioseptectomy	29 (4.7)	27 (4.7)	2 (4.9)	.87
SAS/VSD enlagement	13 (2.1)	13 (2.2)	0 (0.0)	.58
Pacemaker implant	12 (1.9)	11 (1.9)	1 (2.4)	1.00
Fenestration at TCPC	46 (7.4)	41 (7.1)	5 (12.2)	.89
Postoperative data				
ICU stay (days)	6 (4-9)	6 (4-9)	7 (6-11)	.02
Hospital stay (days)	20 (14-28)	20 (14-27)	22(19-33)	.01
Complications				
Pleural effusion	301 (48.5)	274 (47.3)	27 (65.9)	<.01
Chylothorax	131 (21.2)	116 (20.1)	15 (36.6)	<.01
Secondary fenestration	11 (1.8)	8 (1.4)	3 (7.3)	<.01

Abbreviations: AVV, atrioventricular valve; AXC, aortic cross clamp; CPB, cardiopulmonary bypass; DKS, Damus-Kaye-Stansel; ICU, intensive care unit; PA, pulmonary artery; PB, plastic bronchitis; PLE, protein losing enteropathy; SAS, subaortic stenosis; TCPC, total cavopulmonary connection.
[a]*P* value was calculated with Cox-regression model. Variables were presented in N (%) or median (IQR).

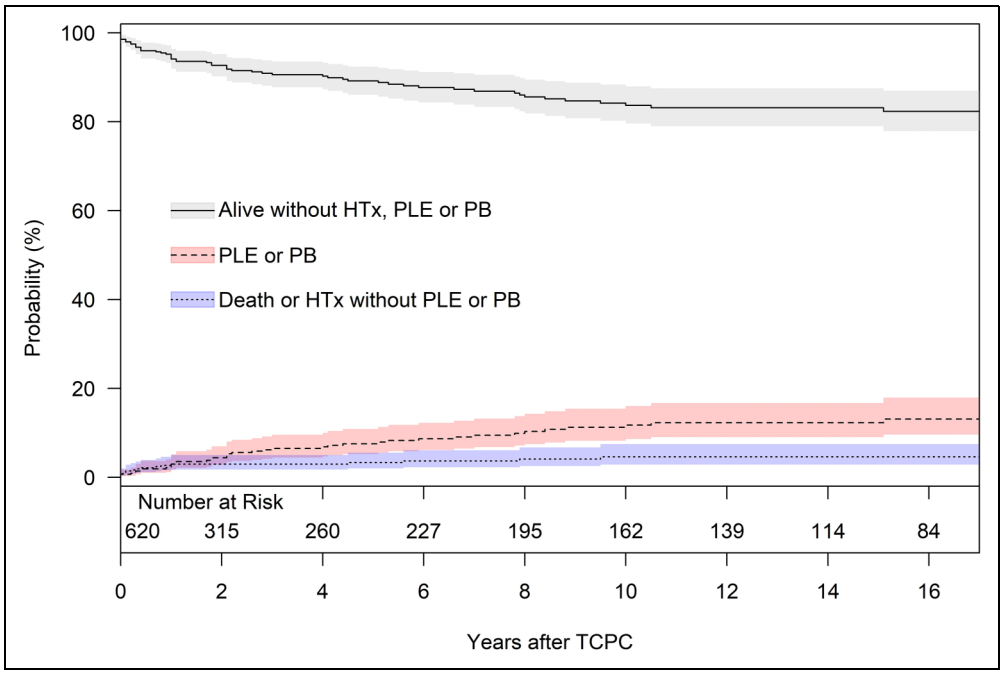

Figure 1. Competing risks plot shows probability of patients who survived the total cavopulmonary connection (TCPC) remaining free of protein-losing enteropathy (PLE) and plastic bronchitis (PB). Outcomes after TCPC: cumulative incidence of PLE/PB (dashed line) and mortality (short dashed line). Patients still living without onset of PLE/PB are indicated by solid line.

Table 3. Risk Factor Analysis for Onset of PLE/PB.

	Univariate			Multivariate		
Variables	*P* value	HR	95% CI	*P* value	HR	95% CI
Dominant RV	**.007**	2.562	1.300-5.049	.021	2.243	1.129-4.458
HLHS	**.005**	2.492	1.325-4.689			
UVH	.647	0.841	0.401-1.764			
DILV	.878	0.934	0.392-2.225			
TA	.126	0.399	0.123-1.294			
UAVSD	.607	1.453	0.350-6.031			
ccTGA	.334	0.046	0.000-23.871			
PAIVS	.433	0.452	0.062-3.291			
Isomerism	.248	1.737	0.680-4.435			
Dextrocardia	.876	0.911	0.281-2.955			
TAPVC/PAPVC	**.036**	2.529	1.062-6.026			
Age at TCPC	.071	0.875	0.758-1.011			
Weight at TCPC	.097	0.952	0.898-1.009			
Fenestration	.891	1.072	0.397-2.893			
Pleural effusion	**.009**	2.361	1.235-4.513	.027	2.101	1.090-4.049
Chylothorax	**.006**	2.448	1.293-4.637			

Abbreviations: ccTGA, congenitally corrected transposition of the great arteries; DILV, double inlet left ventricle; HLHS, hypoplastic left heart syndrome; PA-IVS, pulmonary atresia-intact ventricular septum; PAPVC, partial anomalous pulmonary venous connection; PB, plastic bronchitis; PLE, protein losing enteropathy; RV, right ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TCPC, total cavopulmonary connection; UAVSD, unbalanced atrioventricular septal defect; UVH, univentricular heart.
Values p<0.05 indicator in bold.

at 15 years, the cumulative incidence of death or HTx was 3.2% at 5 years, 4.6% at 10 years, and 4.6% at 15 years, and survival without HTx or PLE/PB was 89.2% at 5 years, 83.7% at 10 years, and 83.1% at 15 years.

Analysis was performed to identify risk factors for onset of PLE/PB. The results of Cox regression model are shown in Table 3. The results of the univariate analysis identified dominant RV (hazard ratio [HR], 2.56; 95% CI, 1.30-5.04), HLHS (HR, 2.49; 95% CI, 1.32-4.68), total (partial) anomalous pulmonary venous connection (TAPVC/PAPVC, HR, 2.52; 95% CI, 1.06-6.02), prolonged pleural effusions after TCPC (HR, 2.36; 95% CI, 1.23-4.51), and chylothorax after TCPC (HR, 2.44; 95% CI, 1.29-4.63) as predictors for developing PLE or PB. Age at TCPC and fenestration was not identified as a predictor. Multivariate analysis revealed dominant RV (HR = 2.24; 95% CI, 1.12-4.45, $P = .021$), and prolonged pleural effusions after TCPC (HR, 2.10; 95% CI, 1.09-4.04, $P = .027$) as independent predictors.

Era analysis was performed. When study periods were divided into two eras before 2008 and after 2009, there was no significant difference between the early and the late era ($P = .200$, HR = 1.569, 95% CI: 0.787-3.127).

Clinical Course and Treatment Strategies After Onset of PLE and PB

In the PLE/PB population, freedom from death or transplantation after PLE/PB diagnosis at 5 and 10 years was 88.7% and 76.4%, respectively (Figure 2). Freedom from death or transplantation after PLE diagnosis at 5 and 10 years was 88.0% and 78.2%, respectively (Supplementary Figure 2), and freedom from death or transplantation after PB was 85.7% and 73.5%, respectively (Supplementary Figure 3). Patients were followed up over a median duration of 5.9 (1.2-13.2) years. The majority of patients with PLE and PB presented symptomatically to the hospital at the time of their primary diagnosis, but thereafter the management was largely on an outpatient basis.

Eleven surgical interventions were performed in 10 patients (Table 3): These were defined as atrioventricular valve repairs (n = 4), Fontan pathway revisions (n = 2), pacemaker implantation (n = 2), secondary fenestration (n = 1), diaphragm plication (n = 1), and ventricular assist device implantation with a newly developed Y-shaped inflow cannula, followed by successful HTx with the resolution of PLE (n = 1).[18] Of those patients who received surgery three patients died, whereas the rest are still alive. In most cases, interventions improved PLE symptoms and protein loss got better. Unfortunately, often PLE symptoms worsened again after time and reintervention was indicated. In nine patients, recovery from PLE with the resolution of PLE symptoms and normal protein levels was achieved. Causes of death were multifactorial.

Subgroup analysis in the PLE/PB population was performed to identify risk factors for death or HTx after the onset of PLE/PB. The results of Cox regression model are shown in Supplementary Table 1. By multivariable analyses, previous pulmonary artery banding (HR, 4.27; 95% CI, 1.13-16.09, $P = .031$) was a predictive factor for mortality or transplantation (Supplementary Tables E1).

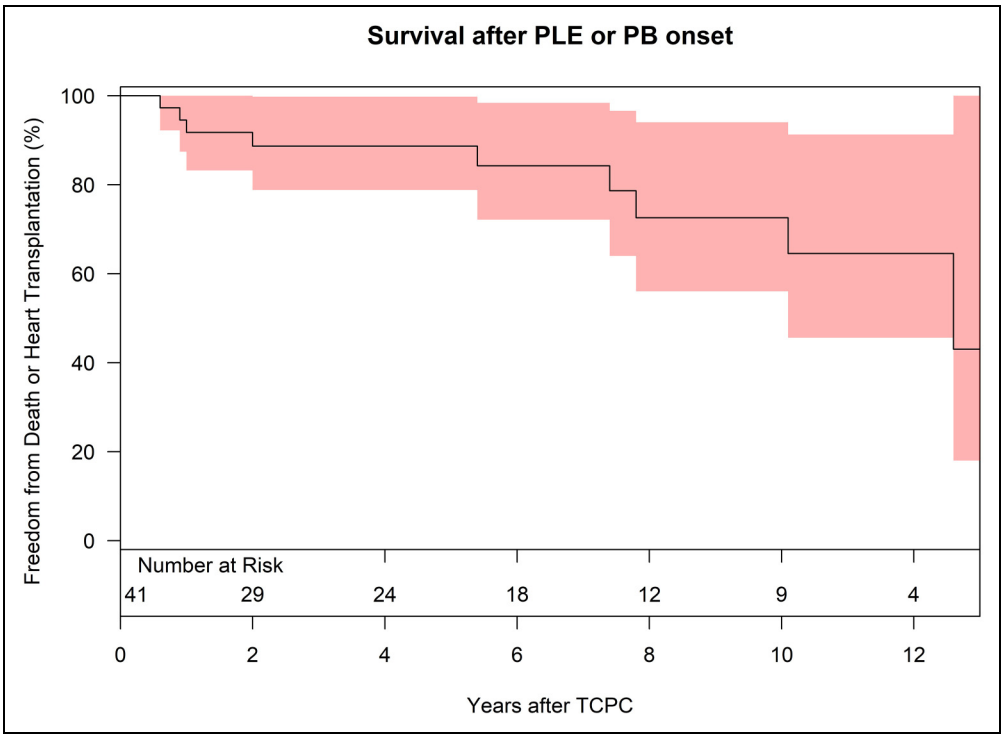

Figure 2. Kaplan-Meier curve showing freedom from death or transplantation after developing protein-losing enteropathy (PLE) or plastic bronchitis (PB).
Abbreviation: TCPC, total cavopulmonary connection.

Discussion

The present study evaluated the incidence of PLE and PB after TCPC. A total of 41 patients developed PLE/PB. Incidence of PLE/PB was 7.7% at 5 years following TCPC. Dominant RV and prolonged pleural effusion after TCPC were identified as independent predictors of onset of PLE and PB. Survival after onset of PLE/PB was 88.7% and 76.4% at 5 years and 10 years, respectively. A total of 11 surgical procedures including one HTx succeeded by right heart bypass were performed and had improved the symptoms.

Protein-losing enteropathy and plastic bronchitis are poor prognostic factors after the Fontan procedure and are one of the primary predictors of death and transplantation in our population. There are variable data regarding the risk of their occurrence, predictors of adverse outcomes in affected patients, and optimal treatments. In the early era in the 1990s, Feldt et al reported a cumulative risk for PLE/PB of 13.4% at 10 years, and 5-year survival rate of 46%, and Mertens, et al reported an incidence of PLE of 3.7% and 46% of mortality after onset of PLE. However, Sharma et al recently reported a prevalence of PLE/PB of 4.9% at 30 years, with freedom from death or transplantation at 5, 10, and 15 years of 70%, 65%, and 43%, respectively.[1] Our results were consistent with the recent report.

We have previously reported outcomes after TCPC surgery at our institution and found that the incidence of late complications, such as tachyarrhythmia or thromboembolic complications had improved as compared with those with classic Fontan procedures.[17] However, the incidence of PLE/PB was not much reduced in the cohort of TCPC. Our incidence of PLE and PB is marginally lower than that of 8% at 15 years by Atz and colleagues[8] and significantly less than that of 13.4% at 10 years reported by Feldt and colleagues.[7] It is likely that the incidence of PLE and PB reflects the health of a given population of patients with Fontan circulation.

In this study, several factors for the development of PLE/PB were identified. We found that patients with dominant RV (13.0% in the overall population and 27.0% in the PLE/PB population), especially with HLHS (13.0% in overall population and 27.0% in the PLE/PB population) had a high incidence of PLE/PB. Bernardi et al also demonstrated dominant RV and HLHS as a risk factor for development of PLE and PB.[19] It was not surprising that risk factors for developing PLE or PB were RV with HLHS morphology, which are likely associated with adverse outcomes.[20] The association of prolonged postoperative pleural effusions with PLE and PB is consistent with etiological risk factors such as elevated venous pressure and decreased cardiac output.[21] Yu et al reported that high Fontan venous pressure and low pulmonary vascular compliance predisposes post-Fontan patients to PLE.[21] Sharma et al could postulate that the older age of Fontan patients may predispose them to the development of systemic pulmonary collaterals, negatively affecting the Fontan circulation.[2] However, age at TCPC was not identified as a predictor for PLE/PB in this study. It might be due to the fact that the median age at the time of the Fontan operation

was lower in our cohort. It seems that we may now be evolving to a stage where we have better control of these complications. Only 25% of the patients died or required HTx in the 5 years after the diagnosis, with the remaining patients staying relatively stable for long periods. The current literature describes these complications as a chronic indolent disease leading to morbidity in terms of wound healing, coagulopathies, bone hypodensity, immune compromise, and growth stagnation. It remains unclear what the best interventions for these patients are and it is persistently difficult to decide at which stage to offer them. The mainstay of treatment remains decreasing fluid overload through aggressive diuresis as noted by Mertens and colleagues.[5]

Transplant may offer a cure. Schumacher et al reported 83% 1-year survival after HTx where nearly all patients reached the resolution of PLE in the recent multicenter study. They demonstrated that PLE severity, duration, and treatment do not influence post-HTx outcome.[14] Heart transplantation may become a good therapy option in the future. On the other side, similar to the findings of Mertens and colleagues,[5] we found surgical intervention to be fraught with high risk.

In this study, we found PAB as a risk factor for mortality/transplant after onset of PLE/PB. Yet we cannot explain why it is a significant risk. In our previous study, PAB was identified as a risk factor for longitudinal ventricular dysfunction after TCPC.[22] However, further analyses are necessary to clarify the exact mechanisms of why PAB influences the mortality after onset of PLE/PB.

Limitation

This study was limited by its retrospective, nonrandomized, and single-center design. Surgical and medical management may have changed during the study period, probably influencing the long-term outcomes and incidence of PLE and PB. Protein-losing enteropathy and PB remain rare conditions, with each clinician seeing a few patients, rendering difficulty in creating diagnosis and management protocols. A strict diagnostic criterion should be set in place, with imaging of the lymphatic system for each patient. These should then correlate with strict medical and surgical intervention protocols (which at present remain speculative) and investigate through further prospective studies.

Conclusions

Protein-losing enteropathy and plastic bronchitis remain severe complications of the Fontan circulation even in the modern era of TCPC. Patients with HLHS, dominant RV, and prolonged pleural effusions, were at higher risk for developing PLE/PB. About 25% of the patients died or required a HTx within 10 years after onset of PLE/PB. The remaining patients recovered or were stable for the long term. Assist device implantation and HTx remain the ultimate treatment for those who are most severely affected by these complications. A newly developed Y-shaped inflow cannula system of the assist device is thought to be promising for improving the results of bridge to HTx.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplemental Material

Supplemental material for this article is available online.

ORCID iD

Alfred Hager https://orcid.org/0000-0002-2481-2017

References

1. Sharma VJ, Iyengar AJ, Zannino D, et al. Protein-losing enteropathy and plastic bronchitis after the Fontan procedure. *J Thorac Cardiovasc Surg*. 2021;161(6):2158-2165.e4.
2. Rychik J, Atz AM, Celermajer DS, et al. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e234-e284. doi:10.1161/CIR.0000000000000696
3. Johnson J, Driscoll D, O'Leary PW. Protein-losing enteropathy and the Fontan operation. *Nutr Clin Pract*. 2012;27(3):375-384.
4. Grutter G, Di Carlo D, Gandolfo F, et al. Plastic bronchitis after extracardiac Fontan operation. *Ann Thorac Surg*. 2012;94(3):860-864.
5. Mertens L, Hagler DJ, Sauer U, et al. Protein-losing enteropathy after the Fontan operation: an international multicenter study. *J Thorac Cardiovasc Surg*. 1998;115(5):1063-1073.
6. John AS, Johnson JA, Khan M, et al. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. *J Am Coll Cardiol*. 2014;64(1):54-62.
7. Feldt RH, Driscoll DJ, Offord KP, et al. Protein losing enteropathy after the Fontan operation. *J Thorac Cardiovasc Surg*. 1996;112(3):672-680.
8. Atz AM, Zak V, Mahony L, et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. *J Am Coll Cardiol*. 2017;69(22):2735-2744.
9. Schleiger A, Ovroutski S, Peters B, et al. Treatment strategies for protein-losing enteropathy in Fontan-palliated patients. *Cardiol Young*. 2020;30(5):698-709.
10. Bauer C, Mair R, Mair R, Tulzer G. Thoracic duct decompression and jugular vein banding-an effective treatment option for protein-losing enteropathy and plastic bronchitis in severe failing Fontan circulation: a case report. *Eur Heart J Case Rep*. 2020;4(5):1-4.
11. António M, Gordo A, Pereira C, Pinto F, Fragata I, Fragata J. Thoracic duct decompression for protein-losing enteropathy in failing Fontan circulation. *Ann Thorac Surg*. 2016;101(6):2370-2373.
12. Hraska V. Decompression of thoracic duct: new approach for the treatment of failing Fontan. *Ann Thorac Surg*. 2013;96(2):709-711.

13. Gierlinger G, Sames-Dolzer E, Kreuzer M, et al. Surgical and interventional rescue strategies for Fontan failure. *Interact Cardiovasc Thorac Surg*. 2022;35(3). doi:10.1093/icvts/ivac098.
14. Schumacher KR, Yu S, Butts R, et al. Fontan-associated protein-losing enteropathy and post-heart transplant outcomes: a multicenter study. *J Heart Lung Transplant*. 2019;38(1):17-25.
15. Sagray E, Johnson JN, Schumacher KR, et al. Protein-losing enteropathy recurrence after pediatric heart transplantation: multicenter case series. *Pediatr Transplant*. 2022;26(5):e14295. doi:10.1111/petr.14295
16. Schreiber C, Hörer J, Vogt M, et al. Nonfenestrated extracardiac total cavopulmonary connection in 132 consecutive patients. *Ann Thorac Surg*. 2007;84(3):894-899.
17. Ono M, Kasnar-Samprec J, Hager A, et al. Clinical outcome following total cavopulmonary connection: a 20-year single-centre experience. *Eur J Cardiothorac Surg*. 2016;50(4):632-641.
18. Michel SG, Menon AK, Haas NA, Hörer J. Cavopulmonary support with a modified cannulation technique in a failing Fontan patient. *Interact Cardiovasc Thorac Surg*. 2022;35(2). doi:10.1093/icvts/ivac090.
19. Bernardi AM, Moses S, Barber BJ, Witte MH, Seckeler MD. Higher incidence of protein-losing enteropathy in patients with single systemic right ventricle. *Pediatr Cardiol*. 2021;42(1):178-181.
20. Alsoufi B, Gillespie S, Kim D, et al. The impact of dominant ventricle morphology on palliation outcomes of single ventricle anomalies. *Ann Thorac Surg*. 2016;102(2):593-601.
21. Yu JJ, Yun TJ, Yun SC, et al. Low pulmonary vascular compliance predisposes post-Fontan patients to protein-losing enteropathy. *Int J Cardiol*. 2013;165(3):454-457.
22. Ono M, Beran E, Burri M, et al. Long-term outcome of preadolescents, adolescents, and adult patients undergoing total cavopulmonary connection. *J Thorac Cardiovasc Surg*. 2018;156(3):1166-1176.e4.