*Cardiology in the Young*

**cambridge.org/cty**

# Incidence, pathophysiology, and treatment of failing Fontan after the total cavopulmonary connection

Paula Gaebert[1,2,3], Thibault Schaeffer[1,2,3], Jonas Palm[4], Chiara Di Padua[1,2,3], Carolin Niedermaier[1,2,3], Nicole Piber[5], Alfred Hager[4], Peter Ewert[4], Jürgen Hörer[1,2,3] and Masamichi Ono[1]

[1]Department of Congenital and Pediatric Heart Surgery, Technische Universität München, German Heart Center Munich, Munich, Germany; [2]Division of Congenital and Pediatric Heart Surgery, University Hospital of Munich, Ludwig-Maximilians-Universität, Munich, Germany; [3]Europäisches Kinderherzzentrum München, Munich, Germany; [4] Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich at the Technical University of Munich, Munich, Germany and [5]Department of Cardiovascular Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany

## Original Article

**Cite this article:** Gaebert P, Schaeffer T, Palm J, Di Padua C, Niedermaier C, Piber N, Hager A, Ewert P, Hörer J, and Ono M (2024) Incidence, pathophysiology, and treatment of failing Fontan after the total cavopulmonary connection. *Cardiology in the Young* **34**: 2406–2413. doi: 10.1017/S1047951124025782

Received: 23 April 2024
Revised: 31 May 2024
Accepted: 31 May 2024
First published online: 3 October 2024

**Keywords:**
Failing fontan; total cavopulmonary connection; ventricular assist device; heart transplantation

**Corresponding author:**
Masamichi Ono; Email: ono@dhm.mhn.de

Paula Gaebert and Thibault Schaeffer contributed equally.

Meeting presentation: Presented at the 60th Annual Meeting of the Society of Thoracic Surgeons, San Antonio, Texas, January 27-29, 2024.

## Abstract

*Background:* Failing Fontan poses a significant clinical challenge. This study aims to improve patients' outcomes by comprehensively understanding the incidence, pathophysiology, risk factors, and treatment of failing Fontan after total cavopulmonary connection. *Methods:* We performed a retrospective analysis of patients who underwent total cavopulmonary connection at the German Heart Center Munich between 1994 and 2022. The onset of failing Fontan was defined as: protein-losing enteropathy, plastic bronchitis, NYHA class IV, NYHA class III for > one year, unscheduled hospital admissions for heart failure symptoms, and evaluation for heart transplantation. *Results:* Among 634 patients, 76 patients presented with failing Fontan, and the incidence was 1.48 per 100 patient-years. Manifestations included protein-losing enteropathy (n = 34), hospital readmission (n = 28), NYHA III (n = 18), plastic bronchitis (n = 16), evaluation for heart transplantation (n = 14), and NYHA IV (n = 4). Risk factors for the onset of failing Fontan were dominant right ventricle ($p = 0.010$) and higher pulmonary artery pressure before total cavopulmonary connection ($p = 0.004$). A total of 72 interventions were performed in 59 patients, including balloon dilatation/stent implantation in the total cavopulmonary connection pathway (n = 49) and embolization of collaterals (n = 24). Heart transplantation was performed in four patients. The survival after the onset of Fontan failure was 77% at 10 years. Patients with failing Fontan revealed significantly higher zlog-NT-proBNP levels after onset compared to those without ($p = 0.021$) *Conclusions:* The incidence of Fontan failure was 1.5 per 100 patient years. Dominant right ventricle and higher pulmonary artery pressure before total cavopulmonary connection were significant risks for the onset of failing Fontan. Zlog-NT-proBNP is only a late marker of Fontan failure.

## Introduction

The Fontan procedure reduces mortality in patients with univentricular hearts and allows them to have life expectancies extending into adulthood. The current standard procedure of choice is the total cavopulmonary connection.[1,2] Despite the remarkable progress, the Fontan operation remains a palliative procedure.[1,2] Therefore, Fontan patients are at lifelong risk of complications, such as systemic ventricular dysfunction, arrhythmias, hypoxia, protein-losing enteropathy, and plastic bronchitis. These complications can lead to a decompensation of the Fontan circulation, known as 'Failing Fontan'.[2–4] Recent studies have estimated the rate of Fontan failure around 7% by the age of 20 years, increasing to 38% by the age of 40 years.[5] The condition manifests in various haemodynamic phenotypes, affecting the cardiovascular system, the intestinal and pulmonary lymphatic system, kidneys, and liver.[6] The treatment strategies vary, including medical therapy, interventional procedures, and surgical rescue strategies.[7,8] Implantation of a ventricular assist device as a bridge to transplant and heart transplantation represents the last therapeutic option; considering the growing population of patients with Fontan circulation due to improved surgical techniques and medical therapy, the issue of failing Fontan becomes increasingly important.[9,10] Previous studies have been performed mainly in adult patients after various types of Fontan procedures, and studies evaluating contemporary total cavopulmonary connection cohort are rare. Therefore, it is essential to detect Fontan failure early, standardise therapies, and develop new treatment strategies. One potential biomarker for improved patient

**Table 1.** Definition of failing Fontan based on six different criteria

| NYHA functional class IV | NYHA functional class III for > one year | Unscheduled hospital admissions for heart failure symptoms | Evaluation/ listing for cardiac transplantation | Active protein-losing enteropathy (PLE) | Active plastic bronchitis (PB) |
|---|---|---|---|---|---|

follow-up and detecting the onset of failing Fontan could be N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is already used in adults as a marker for heart failure.[11,12]

This study aims to comprehensively explore failing Fontan in our cohort of contemporary total cavopulmonary connection patients while focusing on its incidence, underlying pathophysiology, risk factors, and contemporary treatment strategies.

## Methods

### Ethical statement

This study was approved by the Institutional Review Board of the Technical University of Munich (approval number 2023-422-S-KR on the 14th August 2023). Because of the retrospective nature of the study, the need for individual patient consent was waived.

### Patients and data collection

This single-centre retrospective cohort study included all patients who underwent total cavopulmonary connection at the German Heart Center Munich from May 1994 to December 2022. Medical records included baseline morphology and demographics as well as pre-, intra-, and postoperative data using digital and paper chart reviews of each patient. The patients obtained outpatient follow-ups with paediatric cardiologists. The follow-up duration for each patient was defined as the time from total cavopulmonary connection to the date of their last visit. For patients who died, the endpoint of the survey was marked at the time of death.

### Operative techniques

The operative techniques for total cavopulmonary connection were described in previous reports.[13,14] Fenestration was not routinely performed and was only used for high-risk patients, such as those with a one lung Fontan or patients with reduced ventricular function.[13] Lateral tunnel total cavopulmonary connection was performed in 50 patients in the early era. In January 1999, extra-cardiac conduit total cavopulmonary connection was introduced, and it has been our standard procedure since May 2002.[14] Cavopulmonary support techniques with a modified cannulation technique were described in previous reports.[15]

### Diagnosis of failing Fontan

Patients had regular inpatient and outpatient check-ups. The onset of failing Fontan was defined by the following categories (Table 1): postoperative diagnosis of protein-losing enteropathy (ascites with serum albumin <35 g/l) or plastic bronchitis (expectoration of casts), NYHA class IV or NYHA class III for > one year, unscheduled hospital admissions for heart failure symptoms, and evaluation/listing for heart transplantation including ventricular assist device implantation.[16] Unscheduled hospital admissions for heart failure symptoms were defined as unplanned admissions to a hospital with decompensated heart failure necessitating emergent therapy.

### Statistical analysis

Categorical variables are presented as absolute numbers and percentages. A chi-squared test was used for categorical data. Continuous variables are expressed as medians with interquartile ranges. Normally distributed variables were compared using an independent sample *t*-test. For those not adhering to normal distribution, the Mann–Whitney *U* test was utilised. Due to the highly age-dependent reference intervals, age-adjusted zlog values were used for NT-proBNP (abbreviated as "zlog-NT-proBNP"), which are interpreted in the same way as common *z*-scores.[17] NT-proBNP data were collected at various time points and compared using its age-adjusted zlog value. A competitive risk analysis for onset of failing Fontan and death/transplantation was performed. Pre- and perioperative factors associated with the onset of failing Fontan were identified using Cox regression models. Factors used in the analysis are shown in Supplementary Table S1. Transplant-free survival after onset of failing Fontan was estimated using the Kaplan–Meier method. Data analysis was performed using SPSS version 28.0 for Windows (IBM, Ehningen, Germany) and *R*-statistical software (state package and cmprsk package).

## Results

### Patient characteristics and perioperative data

A total of 634 patients were included with a median follow-up of 5.5 years, and 76 patients developed failing Fontan during a median period of 3.6 years after total cavopulmonary connection. Manifestations included protein-losing enteropathy in 34, hospital readmission in 28, NYHA III for > one year in 18, plastic bronchitis in 16, evaluation for heart transplantation in 14, and NYHA IV in four patients. The competing plots of death and Fontan failure are shown in Figure 1. The total incidence of failing Fontan over the entire observation time was 1.48 per 100 patient-years. Patient characteristics with and without failing Fontan are presented in Table 2. In patients who developed failing Fontan, the median age (2.7 vs. 2.3 years, $p = 0.028$) was older and weight (12.2 vs. 12.0 kg, $p = 0.027$) at total cavopulmonary connection was higher compared to those who did not. The patients who developed failing Fontan had a higher prevalence of dominant right ventricle (65.8 vs. 50.7%, $p = 0.014$), heterotaxy (15.8 vs. 6.6%, $p = 0.005$), and total/partial anomalous pulmonary venous drainage (Total anomalous pulmonary venous connection/Partial anomalous pulmonary venous connection, 14.5 vs. 5.6%, $p = 0.003$). Regarding the initial palliation, patients experiencing Fontan failure had more often pulmonary artery banding compared to those who did not (25.0% vs. 13.1%, $p = 0.006$). Cardiac catheterisation data before total cavopulmonary connection are shown in Supplementary Table S2. Median pulmonary artery pressure (10 vs. 9 mmHg, $p < 0.001$) and trans-pulmonary gradient (4 vs. 4 mmHg, $p = 0.003$) were higher in patients who developed failing Fontan compared to those who did not. When pulmonary artery pressure was compared between 92 patients who underwent pulmonary artery banding and 542 patients who did not, median pulmonary artery pressure was significantly higher in patients who underwent pulmonary artery banding (11 vs. 9 mmHg, $p < 0.001$).

https://doi.org/10.1017/S1047951124025782 Published online by Cambridge University Press

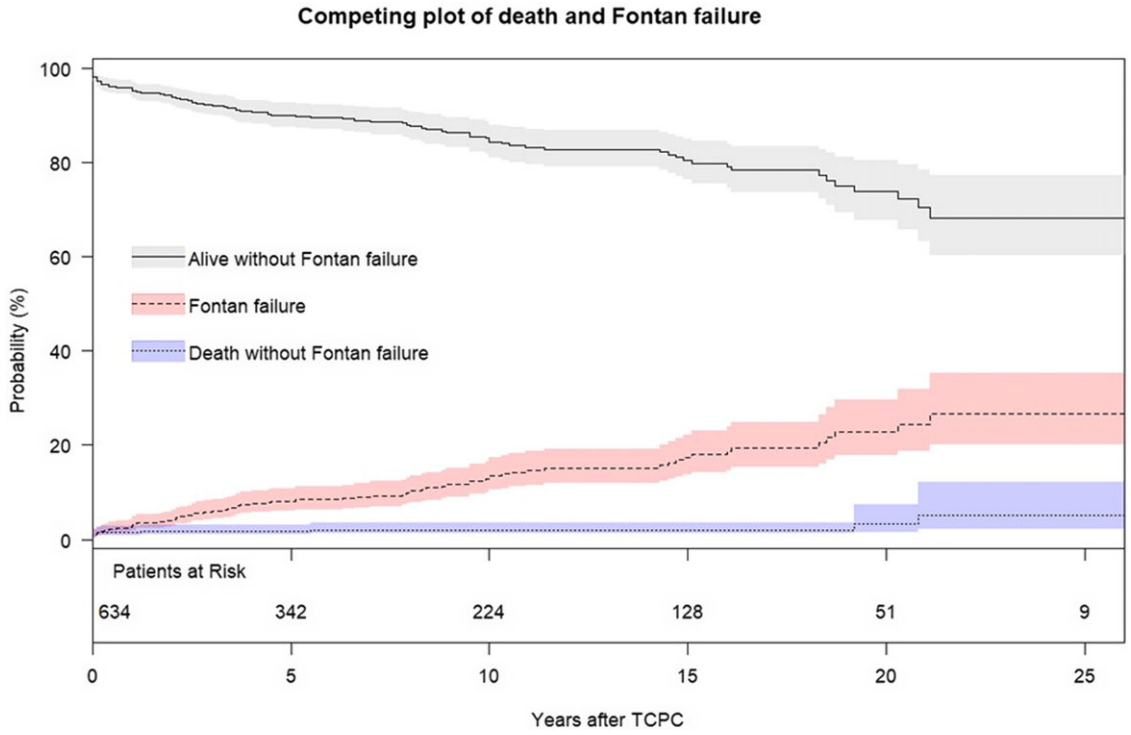


**Figure 1.** Outcome after total cavopulmonary connection (TCPC): cumulative incidence of failing Fontan (red) and mortality (blue). The gray curve indicates patients who survived TCPC without experiencing the onset of failing Fontan.

Perioperative data are depicted in Table 3. In patients who developed failing Fontan, the diameter for the extra-cardiac conduit was larger ($p = 0.013$), median cardiopulmonary bypass time was longer (77 vs. 66 minutes, $p = 0.044$), and more concomitant procedures were performed (42.1 vs. 24.0%, $p < 0.001$), compared to those without Fontan failure. In particular, pulmonary artery reconstruction was more frequently performed in patients who developed failing Fontan, compared to those without Fontan failure (19.7 vs. 8.1%, $p = 0.001$). When the prevalence of pulmonary artery reconstruction was compared between older patients (age at total cavopulmonary connection older than 2.7 years, n = 213) and younger patients (age at total cavopulmonary connection of 2.7 years or younger, n = 421), it was more frequent in older patients (18.3 vs. 5.0%, $p < 0.001$). Postoperatively, patients with failing Fontan showed prolonged median stays in the intensive care unit (7 vs. 6 days, $p = 0.038$) and in the hospital (23 vs. 19 days, $p = 0.004$) compared to those without failing Fontan. Furthermore, the incidence of ascites requiring drainage in the ICU (28.9 vs. 17.7%, $p = 0.019$) and the need for secondary fenestration (5.3 vs. 1.3%, $p = 0.012$) were higher in patients experiencing Fontan failure.

### *Risk factor analysis*

The results are shown in Supplementary Tables S1 and S3. The multivariate analysis identified dominant right ventricle ($p = 0.010$, hazard ratio: 2.062, 95% CI: 1.192–3.568) and higher pulmonary artery pressure before total cavopulmonary connection ($p = 0.004$, HR: 1.107, 95% CI: 1.032–3.568) as independent factors associated with the onset of failing Fontan.

### *Therapy and results after onset of failing Fontan*

Medical therapy was performed according to the consultant paediatric cardiologists, included diuretics in 67 patients, phosphodiesterase type 5 inhibitors in 35, angiotensin-converting enzymes inhibitors/Angiotensin1-Antagonists in 30, beta-blocker in 21, glucocorticoids in 16, anti-arrhythmic drugs in 14, endothelin receptor antagonists in eight, and sodium glucose-linked transporter 2 (SGLT-2) Inhibitors in seven. A total of 72 interventions were performed in 59 patients. The details are shown in Supplementary Table S4. Surgical interventions included eight pacemaker implantations, eight atrioventricular valve procedures, three secondary fenestrations, and one resection of sub-aortic stenosis. Heart transplantation was performed in four patients. Among them, one patient underwent ventricular assist device implantation with a newly developed *Y*-shaped inflow cannula, followed by successful heart transplantation. The transplant-free survival after onset of Fontan failure was 86% at 5 years and 77% at 10 years (Figure 2).

### *NT-proBNP value*

Zlog-NT-proBNP levels before and after onset of failing Fontan are shown in Figure 3. While values before the onset of failing Fontan were similar between the patients who developed failing Fontan and those who did not ($p = 0.508$), after the onset, zlog-NT-proBNP was significantly higher in patients with failing Fontan compared to those without ($p = 0.021$). Zlog-NT-proBNP levels for different types of failing Fontan criteria are shown in Figure 4. Patients with heart failure (NYHA III or IV, heart transplantation evaluated patients) demonstrated elevated zlog-NT-proBNP levels, while patients with protein-losing enteropathy and plastic bronchitis did not show elevated zlog-NT-proBNP levels.

### *Comment*

This study demonstrated that failing Fontan was observed in our contemporary cohort of total cavopulmonary connection with an

https://doi.org/10.1017/S1047951124025782 Published online by Cambridge University Press

**Table 2.** Baseline cohort characteristics

| Variables: n (%) or median (IQR) | Total cases | Non-failing Fontan | Failing Fontan | p-value |
|---|---|---|---|---|
| Number of patients | 634 | 558 (88.0) | 76 (12.0) | |
| Age at TCPC (years) | 2.3 (1.8–3.3) | 2.3 (1.8–3.2) | 2.7 (1.8–5.4) | **0.028** |
| Weight at TCPC (kg) | 12.0 (10.7–14.0) | 12.0 (10.7-–14.0) | 12.2 (10.8–19.9) | **0.027** |
| Primary diagnosis | | | | |
| HLHS | 173 (27.3) | 149 (26.7) | 24 (31.6) | 0.371 |
| Univentricular heart (UVH) | 132 (20.8) | 115 (20.6) | 17 (22.4) | 0.723 |
| Tricuspid atresia (TA) | 98 (15.5) | 91 (16.3) | 7 (9.2) | 0.108 |
| DILV | 93 (14.7) | 83 (14.9) | 10 (13.2) | 0.691 |
| PAIVS | 33 (5.2) | 31 (5.6) | 2 (2.6) | 0.282 |
| ccTGA | 32 (5.0) | 29 (5.2) | 3 (3.9) | 0.641 |
| UAVSD | 25 (3.9) | 21 (3.8) | 4 (5.3) | 0.529 |
| Others | 49 (7.7) | 40 (7.2) | 9 (11.8) | 0.152 |
| Dominant right ventricle (RV) | 333 (52.5) | 283 (50.7) | 50 (65.8) | **0.014** |
| Associated cardiac anomaly | | | | |
| TGA | 212 (33.4) | 183 (32.8) | 29 (38.2) | 0.353 |
| DORV | 83 (13.1) | 72 (12.9) | 11 (14.5) | 0.703 |
| CoA | 80 (12.6) | 72 (12.9) | 8 (10.5) | 0.558 |
| Dextrocardia/Situs Inversus | 57 (9.0) | 48 (8.6) | 9 (11.8) | 0.354 |
| Heterotaxy | 49 (7.7) | 37 (6.6) | 12 (15.8) | **0.005** |
| TAPVC/PAPVC | 42 (6.6) | 31 (5.6) | 11 (14.5) | **0.003** |
| Systemic venous return anomaly | 61 (9.6) | 50 (9.0) | 11 (14.5) | 0.126 |
| Palliation and pre-Fontan condition | | | | |
| Norwood/DKS | 271 (42.7) | 234 (41.9) | 37 (48.7) | 0.265 |
| AP-Shunt | 186 (29.3) | 165 (29.6) | 21 (27.6) | 0.210 |
| PAB | 92 (14.5) | 73 (13.1) | 19 (25.0) | **0.006** |
| Number of palliative surgeries | 1 (1–2) | 1 (1–2) | 1 (1–2) | 0.615 |
| Prior BCPS | 585 (92.3) | 517 (92.7) | 68 (89.5) | 0.330 |
| Age at BCPS (months) | 5.2 (3.6–10.0) | 5.0 (3.5–9.2) | 6.8 (4.6–17.2) | 0.459 |
| Weight at BCPS (kg) | 5.7 (4.9–7.2) | 5.6 (4.9–7.1) | 6.2 (4.9–7.7) | 0.420 |

TCPC = total cavopulmonary connection, HLHS = hypoplastic left heart syndrome, DILV = double inlet left ventricle; PAIVS = pulmonary atresia and ventricular septum; TGA = transposition of the great arteries, ccTGA = congentially corrected TGA, UAVSD = unbalanced atrioventricular septal defect, DORV = double outlet right ventricle CoA = coarctation of the aorta; T(P)APVC = total (partial) anomalous pulmonary venous connection, AP = aorto-pulmonary, PAB = pulmonary artery banding, BCPS = bidirectional cavopulmonary shunt, TAPVC = total anomalous pulmonary venous connection, PAPVC = partial anomalous pulmonary venous connection.

incidence of 1.48 per 100 patient-years, with protein-losing enteropathy emerging as the predominant manifestation. Dominant right ventricle and higher pulmonary artery pressure before total cavopulmonary connection were significant risks for failing Fontan. Survival after onset of failing Fontan was 77% at 10 years. Zlog-NT-proBNP was significantly higher in patients with certain types of failing Fontan criteria, not before, but after the onset of symptoms.

### *Incidence and manifestation of failing Fontan*

Several studies with large cohorts of adult Fontan patients investigated the incidence of failing Fontan. Kramer et al. found a 19.6% incidence at 20 years in 198 patients, with the primary manifestation being heart failure (56%), while protein-losing enteropathy was observed in 27%.[16] Dennis et al. involving 683 patients reported freedom from failing Fontan in 93% at age 20 and 77% at age 30, with heart failure being the predominant manifestation and protein-losing enteropathy reported in only 10 patients.[5] Our study aligns with previous research, showing freedom from failing Fontan at 75% after 20 years postoperatively. However, a notable difference is that protein-losing enteropathy emerged as the most common manifestation in our study, in contrast to previous findings. This discrepancy may be attributed to differences in patient cohorts, as our study included approximately 30% of patients diagnosed with hypoplastic left heart syndrome. The cohorts in previous studies encompassed patients operated on in an older era. Our earlier investigation demonstrated that introducing total cavopulmonary connection did not reduce the incidence of protein-losing enteropathy.[18] These

https://doi.org/10.1017/S1047951124025782 Published online by Cambridge University Press

**Table 3.** Perioperative variables

| Variables | Total | Non-failing Fontan | Failing Fontan | p-value |
|---|---|---|---|---|
| | 634 | 558 (88.0) | 76 (12.0) | |
| **Operative data** | | | | |
| Type of TCPC | | | | |
| Intracardiac | 50 (7.9) | 42 (7.5) | 8 (10.5) | 0.363 |
| Extra-cardiac | 584 (92.1) | 516 (92.5) | 68 (89.5) | |
| Conduit diameter (mm) | | | | |
| 14 | 1 (0.2) | 1 (0.2) | 0 (0.0) | **0.013** |
| 16 | 9 (1.5) | 9 (1.7) | 0 (0.0) | |
| 18 | 502 (86.0) | 451 (87.4) | 51 (75.0) | |
| 20 | 57 (9.8) | 44 (8.5) | 13 (19.1) | |
| 22 | 15 (2.6) | 11 (2.1) | 4 (5.9) | |
| CPB time (minutes) | 67 (48–101) | 66 (47–99) | 77 (51–123) | **0.044** |
| Aortic cross clamp (AXC) | 163 (25.7) | 137 (24.6) | 26 (34.2) | 0.071 |
| AXC time (minutes) | 46 (26–73) | 43 (26–73) | 53 (28–79) | 0.663 |
| Fenestration at TCPC | 56 (8.8) | 47 (8.4) | 9 (11.8) | 0.324 |
| Concomitant procedure | 166 (26.2) | 134 (24.0) | 32 (42.1) | <**0.001** |
| DKS | 17 (2.7) | 11 (2.0) | 6 (7.9) | **0.003** |
| AVV procedure | 79 (12.5) | 67 (12.0) | 12 (15.8) | 0.349 |
| PA reconstruction | 60 (9.5) | 45 (8.1) | 15 (19.7) | **0.001** |
| Atrioseptectomy | 30 (4.7) | 25 (4.5) | 5 (6.6) | 0.419 |
| SAS/VSD enlagement | 13 (2.1) | 13 (2.3) | 0 (0.0) | 0.179 |
| Pacemaker implant | 12 (1.9) | 9 (1.6) | 3 (3.9) | 0.161 |
| **Postoperative data** | | | | |
| ICU stay (days) | 6 (4–9) | 6 (4–8) | 7 (6–12) | **0.038** |
| Hospital stay (days) | 20 (14–27) | 19 (14–27) | 23 (18–34) | **0.004** |
| Complications | | | | |
| Pleural effusion | 305 (48.6) | 261 (47.2) | 44 (58.7) | 0.062 |
| Chylothorax | 137 (21.9) | 119 (21.6) | 18 (24.0) | 0.637 |
| Ascites | 120 (19.0) | 98 (17.7) | 22 (28.9) | **0.019** |
| Secondary fenstration | 11 (1.7) | 7 (1.3) | 4 (5.3) | **0.012** |

Variables were presented in n(%) or median (IQR).
RV= right ventricle, LV= left ventricle, TCPC= total cavopulmonary connection; CPB= cardiopulmonary bypass; AXC= aortic cross clamp; DKS= Dames-Kaye-Stansel anatomosis; AVV= atrioventricular valve; PA= pulmonary artery; SAS= subaortic stenosis; VSD= ventricular septal defect.

findings underscore the global challenge in managing an increasing population of failing Fontan patients in the current cohort.

### *Mode, mechanisms, and risks of failing Fontan*

When the Fontan circulation fails, there are very typical well-defined symptoms: reduced exercise capacity; atrial arrhythmia; pleural effusions, ascites; protein-losing enteropathy; plastic bronchitis; thromboembolism; pulmonary veno-venous fistulae, and Fontan-associated liver disease.[19] The mechanisms that cause symptoms are variable from simple mechanisms to complex ones. When failing Fontan is caused by simple mechanisms, such as Fontan pathway stenosis, surgical/catheter interventions improve the symptoms. Cyanosis caused by pulmonary veno-venous collaterals could dramatically improve through coil embolisation of the fistula. When anatomical issues, such as atrioventricular valve regurgitation, aortic valve insufficiency, or aortic coarctation are the underlying mechanisms, symptoms might be improved after surgical interventions. However, the main issues in the context of failing Fontan are "pulmonary vascular resistance" and "systemic ventricular function". Therefore, it is of tremendous importance in patients with threatening Fontan circulatory failure to analyse which part of the "Fontan engine" is not working optimally.[19] When the mechanism is increased pulmonary artery pressure, all the venous congestive symptoms of Fontan circulatory failure might occur. It is a risk for pulmonary veno-venous collaterals, which cause cyanosis. The lymphatic pathways are obstructed, resulting in the development of PLE and PB.

https://doi.org/10.1017/S1047951124025782 Published online by Cambridge University Press

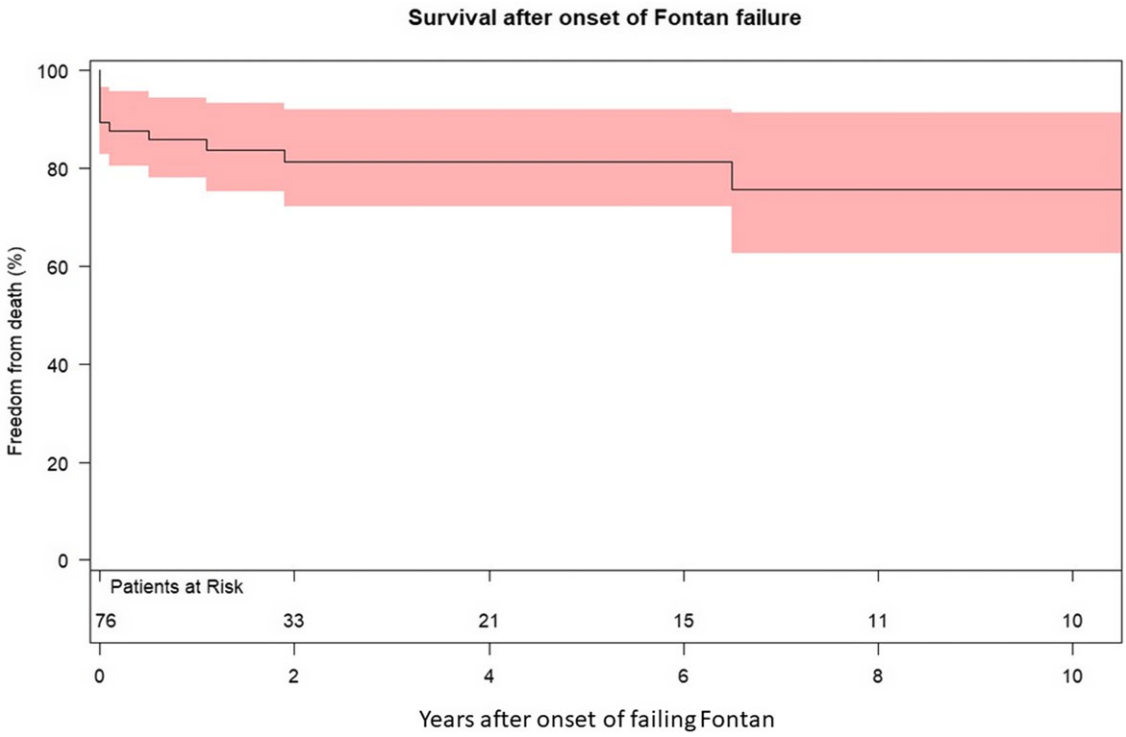


**Figure 2.** Kaplan–Meier curve showing freedom from death or transplantation after developing failing Fontan.

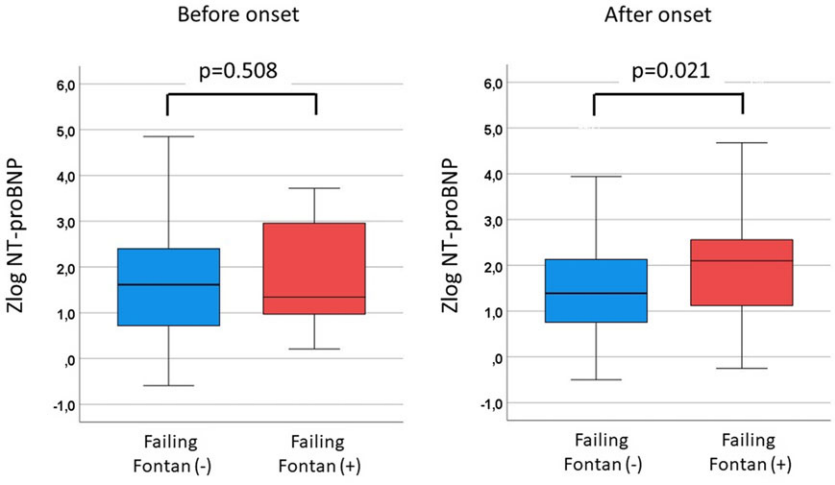


**Figure 3.** Box-and whiskers plots showing zlog-NT-proBNP values in patients with and without failing Fontan.

The elevated pulmonary artery pressure affects negatively in the cardiac return, which might cause diastolic dysfunction of the systemic ventricle. In the older Fontan patients, diastolic system ventricular failure is the dominant cause of Fontan failure.[20] The age-dependent loss in left ventricular compliance seems to be especially detrimental in the long term. Medical therapy is essential, focusing on meticulous treatment of arterial hypertension, possibly targeting an optimal blood pressure range.[19] Lastly, surgical options such as assist device implantation and heart transplantation also play significant roles in the management of ventricular failure.[21]

In this study, dominant right ventricle and higher pulmonary artery pressure before total cavopulmonary connection were identified as risk factors for the development of failing Fontan. It is of note that patients who underwent pulmonary artery banding had significantly higher pulmonary artery pressure before total cavopulmonary connection compared to those who did not. Recent studies have shown that having a dominant right ventricle is not associated with an increased risk of mortality after total cavopulmonary connection. However, patients with dominant right ventricle appear to have more postoperative morbidities compared to those with a dominant left ventricle. Morphological right ventricle and tricuspid valve are not suitable for maintaining systemic circulation. Therefore, patients with dominant right ventricle might progress ventricular dysfunction earlier than those with dominant left ventricle, which consequently means, that patients with dominant right ventricle need special care for late complications. Higher pulmonary artery pressure before total cavopulmonary connection was identified as the strongest risk for the onset of failing Fontan, and it is not surprising. It is well-known

https://doi.org/10.1017/S1047951124025782 Published online by Cambridge University Press

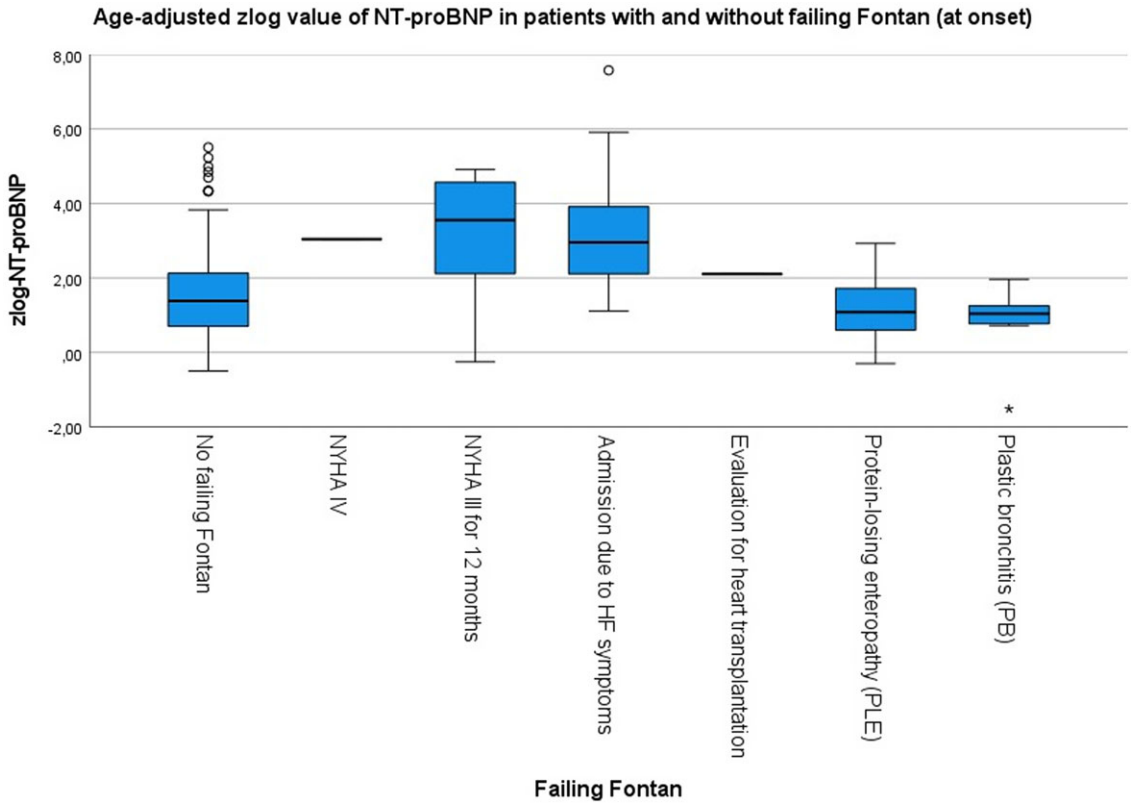


**Figure 4.** Box-and whiskers plots showing zlog-NT-proBNP values in patients with failing Fontan regarding the cause of onset.

that high pulmonary artery pressure before the Fontan procedure is a risk for mortality and morbidities in any type of Fontan procedure. In this contemporary cohort of total cavopulmonary connection, the main manifestations of failing Fontan were protein-losing enteropathy and plastic bronchitis as a consequence of obstructed lymphatic pathways due to high pulmonary artery pressure. In patients with protein-losing enteropathy and plastic bronchitis, ventricular function is usually preserved. Our results demonstrated that the zlog level of NT-pro-BNP was not elevated in these patients. Reducing pulmonary vascular resistance through medical therapy is of high importance. The introduction of lymphatic imaging and interventions during the observation period has paved the way for a more targeted therapeutic approach to address protein-losing enteropathy and plastic bronchitis. Identifying and closing abnormal fistulas through lymphatic interventions has shown symptom resolution for protein-losing enteropathy/plastic bronchitis and is thus a promising treatment option.[22,23] However, these procedures do not address the underlying pathophysiology, the high pulmonary artery pressure, and can therefore only be a symptomatic treatment and no curative approach. In this study, the failing group had placed a larger conduit, which seems counterintuitive. Currently, we use 18 mm Goretex conduit in most patients, and the typical timing for total cavopulmonary connection was 18 months of age and 10 kg. In this study, some patients underwent total cavopulmonary connection at older ages, especially during the early era. These patients tended to have a larger conduit with a diameter of 20 or 22 mm. As failing Fontan develops in a time-dependent manner, we assume that patients who underwent total cavopulmonary connection at older ages with larger conduits in the early era may have a higher prevalence of failing Fontan.

Pulmonary artery reconstruction at total cavopulmonary connection was associated with failing Fontan, and it was more frequently performed in older patients. In the current strategy of staged Fontan palliation of total cavopulmonary connection followed by bidirectional cavopulmonary shunt, waiting for Fontan for the development of the pulmonary artery is not advisable because pulmonary artery size does not significantly increase after bidirectional cavopulmonary shunt[24]. Our previous study demonstrated that a small pulmonary artery size was associated with chylothorax and adverse events after total cavopulmonary connection[25]. Therefore, we assume that a small pulmonary artery might cause the development of a failing Fontan.

### *Future prospective*

Previous studies examining NT-proBNP or BNP as biomarkers for heart failure have had inconsistent results.[26,27] Our results demonstrated that zlog-NT-proBNP increased after the onset of failing Fontan. Although individual values and specific cut-offs may not accurately identify suboptimal Fontan haemodynamics, zlog-NT-proBNP is a useful parameter that may well indicate circulatory deterioration in Fontan patients during longitudinal follow-up, especially in patients with heart failure symptoms. However, it has to be kept in mind that older Fontan types including atrial tissue reveal higher NT-proBNP than patients with extracardiac total cavopulmonary connection.[28]

## Limitations

This study was limited by its retrospective, non-randomized and single-centre design. Surgical and medical management may

https://doi.org/10.1017/S1047951124025782 Published online by Cambridge University Press

have changed during the study period, probably influencing the long-term outcomes. A strict diagnostic criterion for failing Fontan is missing. Serial functional data including echocardiography and MRI are lacking. We did not collect the data of Fontan-associated liver disease, which might affect the development of failing Fontan. Other studies include arrhythmia, heart failure, reduced exercise capacity or Fontan-associated liver disease and report a substantially higher incidence. The study covers a long time period with development of new therapeutic possibilities as lymphatic imaging and interventions, as well as new surgical techniques (e.g. thoracic duct decompression). So current treatment modalities are much more specific as to begin of the study.

## Conclusions

Failing Fontan was observed continuously after total cavopulmonary connection and incidence of Fontan failure was 1.5 per 100 patient-years. Dominant right ventricle and higher pulmonary artery pressure before total cavopulmonary connection were significant risks for late failing Fontan. Surgical and catheter interventions were mandatory for the treatment of failing Fontan. Survival after onset of failing Fontan was 77% at 10 years. Patients with failing Fontan revealed significantly higher zlog-NT-proBNP levels than those without. Zlog-NT-proBNP might become a useful marker for the onset of failing Fontan.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124025782.

**Acknowledgements.** The authors thank Mrs Doris Kienmoser, Dr Takuya Osawa, and Dr Paul Philipp Heinisch, for their help in performing this study.

**Financial support.** This study had no financial support.

**Competing interests.** The authors declare no potential conflicts of interest concerning the research, authorship, or publication of this article.

## References

1. d'Udekem Y, Iyengar AJ, Galati JC et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation 2014; 130: S32–S38.
2. Pundi KN, Johnson JN, Dearani JA Li Z et al. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. J Am Coll Cardiol 2015; 66: 1700–1710.
3. Gewillig M, Brown SC, van de Bruaene A, Rychik J. Providing a framework of principles for conceptualising the Fontan circulation. Acta Paediatr 2020; 109: 651–658.
4. Goldberg DJ, Shaddy RE, Ravishankar C, Rychik J. The failing Fontan: etiology, diagnosis and management. Expert Rev Cardiovasc Ther 2011; 9(6): 785–793.
5. Ghanayem NS, Berger S, Tweddell JS. Medical management of the failing Fontan. Pediatr Cardiol 2007; 28(6): 465–471.
6. Dennis M, Zannino D, du Plessis K et al. Clinical outcomes in adolescents and adults after the Fontan procedure. J Am Coll Cardiol 2018; 71: 1009–1017.
7. Book WM, Gerardin J, Saraf A, Valente AM, Rodriquez 3rdF. Clinical phenotypes of Fontan failure: implications for management. Congenit Heart Dis 2016; 11: 296–308.
8. Gierlinger G, Sames-Dolzer E, Kreuzer M et al. Surgical and interventional rescue strategies for Fontan failure. Interact Cardiovasc Thorac Surg 2022; 35(3): ivac098.
9. van Melle JP, Wolff D, Hörer J et al. Surgical options after Fontan failure. Heart 2016; 102: 1127–1133.
10. Schilling C, Dalziel K, Nunn R et al. The Fontan epidemic: population projections from the Australia and New Zealand Fontan registry. Int J Cardiol 2016; 219: 14–19.
11. Michielon G, van Melle JP, Wolff D et al. Favourable mid-term outcome after heart transplantation for late Fontan failure. Eur J Cardiothorac Surg 2015; 47: 665–671.
12. Law YM, Keller BB, Feingold BM, Boyle GJ. Usefulness of plasma B-type natriuretic peptide to identify ventricular dysfunction in pediatric and adult patients with congenital heart disease. Am J Cardiol 2005; 95: 474–478.
13. Lechner E, Gitter R, Mair R et al. Aminoterminal brain natriuretic peptide levels in children and adolescents after Fontan operation correlate with congestive heart failure. Pediatr Cardiol 2008; 29(5): 901–905.
14. Schreiber C, Hörer J, Vogt M, Cleuziou J, Prodan Z, Lange R. Nonfenestrated extracardiac total cavopulmonary connection in 132 consecutive patients. Ann Thorac Surg 2007; 84: 894–899.
16. 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: 632–641.
16. 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: ivac090.
17. Kramer P, Schleiger A, Schafstedde M et al. A multimodal score accurately classifies Fontan failure and late mortality in adult Fontan patients. Front Cardiovasc Med 2022; 9: 767503.
18. Palm J, Hoffmann G, Klawonn F et al. Continuous, complete and comparable NT-proBNP reference ranges in healthy children. Clin Chem Lab Med 2020; 58: 1509–1516.
19. Hammer V, Schaeffer T, Staehler H et al. Protein-losing enteropathy and plastic bronchitis following the total cavopulmonary connections. World J Pediatr Congenit Heart Surg 2023; 14: 691–698.
20. Hager A. Invasive cardiopulmonary exercise testing in patients with Fontan circulation. J Am Coll Cardiol 2023; 81: 1601–1604.
21. Miranda WR, Borlaug BA, Jain CC et al. Exercise-induced changes in pulmonary artery wedge pressure in adults post-Fontan versus heart failure with preserved ejection fraction and non-cardiac dyspnoea. Eur J Heart Fail 2023; 25(1): 17–25.
22. Kamsheh AM, O'Connor MJ, Rossano JW. Management of circulatory failure after Fontan surgery. Front Pediatr 2022; 10: 1020984.
23. Dori Y, Keller MS, Rome JJ et al. Percutaneous lymphatic embolization of abnormal pulmonary lymphatic flow as treatment of plastic bronchitis in patients with congenital heart disease. Circulation 2016; 133(12): 1160–1170.
24. Smith CL, Dori Y, O'Byrne ML, Glatz AC, Gillespie MJ, Rome JJ. Transcatheter thoracic duct decompression for multicompartment lymphatic failure after Fontan palliation. Circ Cardiovasc Interv 2022; 15: e011733.
25. Staehler H, Schaeffer T, Georgiev S et al. Relationship of aortopulmonary collaterals and pulmonary artery development during staged single ventricle reconstruction. Pediatr Cardiol 2024. DOI: 10.1007/s00246-024-03484-y
26. Kido T, Stern C, Heinisch PP et al. The impact of pulmonary artery size on midterm outcomes after nonfenestrated Fontan operation. J Thorac Cardiovasc Surg 2023; 165: 1651–1660.
27. Cindik N, Gökdemir M, Varan B, Ulubay G, Ozkan M, Tokel NK. Comparison of serum N-terminal pro-brain natriuretic peptide levels, conventional echocardiography, exercise parameters, and dyssynchrony measurements in Fontan patients. Cardiol Young 2023; 33: 1706–1712.
28. Lin HC, Huang SC, Wu MH et al. Preoperative N-terminal pro-brain natriuretic peptide is associated with Fontan outcomes. J Thorac Cardiovasc Surg 2022; 164: 770–780.
29. Bambul Heck P, Muller J, Weber R, Hager A. Value of N-terminal pro brain natriuretic peptide levels in different types of Fontan circulation. Eur J Heart Fail 2013; 15(6): 644–649.