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# A single-institutional experience with 36 children less than 5 kilograms supported with the Berlin Heart: Comparison of congenital versus acquired heart disease

Mark S. Bleiweis, Omar M. Sharaf, Joseph Philip, Giles J. Peek, Yuriy Stukov, Gregory M. Janelle, Andrew D. Pitkin, Kevin J. Sullivan, Connie S. Nixon, Dan Neal, and Jeffrey P. Jacobs

Congenital Heart Center, Departments of Surgery, Pediatrics, and Anesthesiology, University of Florida, Gainesville, FL, USA

## Original Article

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ventricular assist device; congenital heart disease; paediatric heart disease

**Corresponding authors:**
Mark S. Bleiweis;
Email: Bleiweis@ufl.edu;
Jeffrey P. Jacobs;
Email: JeffreyJacobs@ufl.edu

## Abstract

*Objectives:* We reviewed outcomes in all 36 consecutive children <5 kg supported with the Berlin Heart pulsatile ventricular assist device at the University of Florida, comparing those with acquired heart disease (n = 8) to those with congenital heart disease (CHD) (n = 28). *Methods:* The primary outcome was mortality. The Kaplan-Meier method and log-rank tests were used to assess group differences in long-term survival after ventricular assist device insertion. T-tests using estimated survival proportions were used to compare groups at specific time points. *Results:* Of 82 patients supported with the Berlin Heart at our institution, 49 (49/82 = 59.76%) weighed <10 kg and 36 (36/82 = 43.90%) weighed <5 kg. Of 36 patients <5 kg, 26 (26/36 = 72.22%) were successfully bridged to transplantation. (The duration of support with ventricular assist device for these 36 patients <5 kg was [days]: median = 109, range = 4–305.) Eight out of 36 patients <5 kg had acquired heart disease, and all eight [8/8 = 100%] were successfully bridged to transplantation. (The duration of support with ventricular assist device for these 8 patients <5 kg with acquired heart disease was [days]: median = 50, range = 9–130.) Twenty-eight of 36 patients <5 kg had congenital heart disease. Eighteen of these 28 [64.3%] were successfully bridged to transplantation. (The duration of support with ventricular assist device for these 28 patients <5 kg with congenital heart disease was [days]: median = 136, range = 4–305.) For all 36 patients who weighed <5 kg: 1-year survival estimate after ventricular assist device insertion = 62.7% (95% confidence interval = 48.5–81.2%) and 5-year survival estimate after ventricular assist device insertion = 58.5% (95% confidence interval = 43.8–78.3%). One-year survival after ventricular assist device insertion = 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease and 55.6% (95% confidence interval = 39.5–78.2%) in CHD, P = 0.036. Five-year survival after ventricular assist device insertion = 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease and 48.6% (95% confidence interval = 31.6–74.8%) in CHD, P = 0.014. *Conclusion:* Pulsatile ventricular assist device facilitates bridge to transplantation in neonates and infants weighing <5 kg; however, survival after ventricular assist device insertion in these small patients is less in those with CHD in comparison to those with acquired heart disease.

## Introduction

Providing mechanical circulatory support with a ventricular assist device for patients weighing <5 kg presents multiple challenges, and supporting patients weighing <5 kg with congenital heart disease (CHD) is especially complex.[1–14] Over the past four years, our programme has published a series of manuscripts describing our evolving approach to supporting neonates, infants, and children with ventricular assist devices.[15–24] These ten previous publications describe the evolving details of our techniques for ventricular assist device support in neonates, infants, and children with both CHD and acquired heart disease, including the use of "Single Ventricle-Ventricular Assist Device" support in patients with functionally univentricular circulation.

Despite the challenges associated with ventricular assist device support in patients with complex CHD, it is reasonable to strive to achieve outcomes in these challenging patients equivalent to the outcomes achieved after support with a left ventricular assist device or biventricular assist devices in patients with acquired heart disease and biventricular circulation. The purpose of this study is to review our clinical experience in all 36 consecutive children <5 kg at University of Florida who were supported with a pulsatile paracorporeal ventricular assist

device (Berlin EXCOR [Berlin Heart, Inc., Berlin, Germany]) (n = 36) and to compare the characteristics and outcomes of patients with acquired heart disease (n = 8) to the characteristics and outcomes of patients with CHD (n = 28).

## Patients and methods

### Patients

This analysis includes all 36 consecutive patients who weighed <5 kg at the time of ventricular assist device insertion who were supported with the Berlin Heart pulsatile ventricular assist device at the University of Florida, with the first patient cannulated on October 19, 2009, and the most recent patient in this consecutive series cannulated on November 1, 2021. Of these 36 consecutive patients, 8 patients with acquired heart disease and biventricular circulation were supported with ventricular assist device, and 28 consecutive patients with CHD were supported with ventricular assist device, including 5 with biventricular circulation and 23 with functionally univentricular circulation.

Of eight patients with acquired heart disease, all had biventricular circulation. The following fundamental diagnoses were present in these eight patients with biventricular circulation and acquired heart disease:

- Cardiomyopathy (n = 7), or
- Myocarditis (n = 1 [This single patient with myocarditis and biventricular circulation underwent two separate episodes of support with the Berlin Heart, only the first of which is included in this current analysis of 36 children smaller than 5 kg supported with the Berlin Heart over 12 years. This infant was initially cannulated with Berlin Heart biventricular assist devices at 46 days of age and 4.1 kg; after 39 days of ventricular assist device support, the child underwent successful cardiac transplantation. Then, 615 days after the initial heart transplant, this child was again cannulated with Berlin Heart biventricular assist devices at 700 days of age and 11.1 kg {secondary to chronic allograft rejection}; after 13 days of ventricular assist device support, the child underwent successful cardiac retransplantation and is currently alive at the time of submission of this manuscript at 9 years of age.])

Of 28 patients with CHD, 5 had biventricular circulation and 23 had functionally univentricular circulation. The following fundamental diagnoses were present in the five patients with biventricular circulation and CHD:

- Coronary artery stenosis (n = 1),
- Status post repair of tetralogy of Fallot with left ventricular failure (n = 1),
- Status post repair of truncus arteriosus with interrupted aortic arch (n = 1),
- Hypoplastic aortic isthmus, supravalvar aortic stenosis, reduced left ventricular function (n = 1), or
- Status post resection of cardiac rhabdomyoma (n = 1).

Of 23 patients with functionally univentricular circulation, 12 (12/23 = 52.2%) high-risk functionally univentricular patients had hypoplastic left heart syndrome or hypoplastic left heart syndrome-related malformations with ductal-dependent systemic circulation, and 11 (11/23 = 47.8%) high-risk functionally univentricular patients had hypoplastic right heart syndrome or hypoplastic right heart syndrome-related malformations with ductal-dependent pulmonary circulation. Of 12 patients with hypoplastic left heart syndrome or hypoplastic left heart syndrome-related malformations with ductal-dependent systemic circulation, 9 high-risk patients underwent primary hybrid + single ventricle-ventricular assist device insertion without prior cardiac surgery; detailed analyses of these 9 patients have been published.[17] During the same era that these 9 high-risk patients with hypoplastic left heart syndrome or hypoplastic left heart syndrome-related malformations with ductal-dependent systemic circulation underwent primary hybrid + single ventricle-ventricular assist device insertion, 62 standard-risk patients underwent Norwood (Stage 1) at the University of Florida with an operative mortality of 3.2% (2/62).[20] The remaining three patients in this current manuscript with hypoplastic left heart syndrome or hypoplastic left heart syndrome-related malformations underwent ventricular assist device insertion after having undergone:

- Norwood (Stage 1) (n = 2), or
- Hybrid (Stage 1) (n = 1).

Of 11 patients with hypoplastic right heart syndrome or hypoplastic right heart syndrome-related malformations with ductal-dependent pulmonary circulation, 7 high-risk patients with pulmonary atresia and intact ventricular septum underwent primary palliation + single ventricle-ventricular assist device insertion without prior cardiac surgery; detailed analyses of the first 6 of these patients have been published,[19] and 1 additional patient with pulmonary atresia and intact ventricular septum has been managed with this approach since that time. The remaining four patients with hypoplastic right heart syndrome or hypoplastic right heart syndrome-related malformations with ductal-dependent pulmonary circulation underwent ventricular assist device insertion after having undergone:

- Central shunt (n = 2), or
- No interventions prior to ventricular assist device implantation (n = 2).

### Surgical technique, management of ventricular assist devices, and protocols for anticoagulation

Our surgical techniques for ventricular assist device insertion and our detailed protocols for anticoagulation have been published.[18] Patients with functionally univentricular anatomy and physiology are supported with single ventricle-ventricular assist device, which includes an inflow cannula in the common atrium or systemic ventricle and an outflow cannula in a systemic artery (either the ascending aorta or the main pulmonary artery in patients with ductal-dependent systemic circulation and hypoplastic ascending aorta), in the setting of parallel pulmonary flow. Patients with biventricular anatomy and physiology are supported with biventricular assist devices or a left ventricular assist device. Biventricular assist device support uses inflow cannulas in the right atrium and left ventricle with outflow cannulas in the pulmonary artery and aorta, respectively, while left ventricular assist device support uses an isolated inflow cannula in the left ventricle and an isolated outflow cannula in the aorta.

Our programmatic philosophy for providing ventricular assist device support to children, and especially to neonates and infants with biventricular hearts, is to use biventricular assist devices rather than a left ventricular assist device, especially if any evidence

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of biventricular dysfunction exists. Because of the challenges associated with predicting the development of right ventricular failure in patients supported with left ventricular assist device,[25] as well as our low rate of complications with biventricular assist devices combined with the length of time that we often need to wait for a suitable donor heart, our institutional preference is for biventricular assist devices, especially in smaller children, unless right ventricular function is clearly normal.

Our programmatic philosophy for providing single ventricle-ventricular assist device support to functionally univentricular neonates with unfavourable cardiac anatomy and extreme risk of cardiac compromise before or during staged palliation includes the use of primary pre-emptive single ventricle-ventricular assist device support in select high-risk neonates who have either ductal-dependent pulmonary circulation or ductal-dependent systemic circulation. Neonates with functionally univentricular ductal-dependent pulmonary circulation undergo combined palliation + single ventricle-ventricular assist device insertion, while neonates with functionally univentricular ductal-dependent systemic circulation undergo combined hybrid + single ventricle-ventricular assist device insertion. Palliation + single ventricle-ventricular assist device for patients with ductal-dependent pulmonary circulation includes single ventricle-ventricular assist device insertion plus stent placement in the arterial duct or systemic-to-pulmonary artery shunt with pulmonary arterioplasty, if needed. Hybrid + single ventricle-ventricular assist device for patients with ductal-dependent systemic circulation includes single ventricle-ventricular assist device insertion plus application of bilateral pulmonary artery bands, stent placement in the arterial duct, and atrial septectomy, if needed.

The ventricular assist device rate is gradually increased as needed to ensure adequate cardiac output and systemic tissue perfusion. The patient is extubated as soon as possible. Appropriate weight gain and end-organ function are maintained on ventricular assist device support until transplantation.

During the first 24 hours after ventricular assist device insertion, no anticoagulation is given (with the exception of patients with a systemic-to-pulmonary artery shunt who receive aspirin on the initial night of single ventricle-ventricular assist device insertion, as described below). The following anticoagulation protocol is then initiated:

- Bivalirudin: Bivalirudin is initiated on postoperative day 1. During hours 24–72, bivalirudin is titrated to a partial thromboplastin time of 50–70 seconds. After 72 hours, bivalirudin is titrated to a partial thromboplastin time of 70–100 seconds.
- Aspirin: For patients with a systemic-to-pulmonary artery shunt, aspirin is started on the initial night of ventricular assist device insertion at a dose of 5 mg/kg/day (divided into two daily doses), and aspirin is increased each week until a dose of 30 mg/kg/day is reached by week 4. For patients without a systemic-to-pulmonary artery shunt, aspirin is started on day 5 after ventricular assist device implantation at a dose of 5 mg/kg/day (divided into two daily doses), and aspirin is increased each week until a dose of 30 mg/kg/day is reached by week 4.
- Dipyridamole: Dipyridamole is started on week 5 after ventricular assist device implantation at a dose of 2.5 mg/kg/day, and dipyridamole is increased twice each week until a dose of 15 mg/kg/day is reached by week 6.
- Omega-3 fatty acid: Omega-3 fatty acid is typically started at 3–4 months after ventricular assist device implantation.

### Nomenclature and definitions

In this manuscript, patients are divided into the two groups of "acquired" and "congenital." We acknowledge that one may debate whether it is appropriate to classify some forms of cardiomyopathy as "acquired," because some forms of cardiomyopathy are (potentially) associated with newborn errors such as gene mutation, which are strictly speaking "congenital defects". However, to remain consistent with previously published analyses, for the purposes of this analysis, all forms of cardiomyopathy and myocarditis were classified as "acquired." It is a fact that our analysis assigns the classification of "acquired" to "structurally normal" hearts and our analysis assigns the classification of "congenital" to "congenitally malformed" hearts. Although this strategy of classification can be debated because some forms of cardiomyopathy are caused by inborn errors of genetics or metabolism, we retain this system of classification to be consistent with previously published analyses.

In this manuscript, the complication of bleeding includes all patients with surgical bleeding requiring reoperation, as well as all patients with any significant form of bleeding requiring transfusion, including gastrointestinal bleeding. In this manuscript, we used a generous definition of stroke designed to capture all potential strokes. For this analysis, we defined stroke as any confirmed neurologic deficit of abrupt onset caused by a disturbance in blood flow to the brain, when the neurologic deficit is associated with radiographic confirmation by computerized tomographic scanning (CT scan). In our series, none of these reported strokes were life-threatening or necessitated ventricular assist device removal, and some of these strokes were not associated with any long-term neurological deficits.

### Statistics and institutional review board approval

Descriptive summaries of the data were tabulated using mean with standard deviation and median with range. The primary outcome of interest was mortality. The Kaplan-Meier method and log-rank tests were used to assess group differences in long-term survival after ventricular assist device insertion. "Time zero" for this analysis was the time of ventricular assist device insertion, so all survival estimates are estimates of survival after ventricular assist device insertion. To compare groups at specific time points, Z-tests were performed using the Kaplan-Meier estimated survival rates and standard errors at each time point. All analyses were performed using the R statistical software package (V.4.1.1, the R Foundation for Statistical Computing). A P-value = 0.05 was considered statistically significant.

Data were sourced from a registry and database that uses software certified by the Society of Thoracic Surgeons Congenital Heart Surgery Database and has been prospectively maintained on all patients undergoing paediatric and congenital cardiac surgery at our institution (a component of the CardioAccess International Clinical Outcomes Database: Comprehensive Cardiovascular and Thoracic Module, CardioAccess Incorporated, Saint Petersburg, Florida, and Fort Lauderdale, Florida: http://www.cardioaccess.com). This study was approved by the University of Florida Institutional Review Board with waiver of the need for consent: IRB202102055, approved 9/15/2021 and IRB202102664, approved 3/18/2022.

## Results

At the University of Florida, of all 82 patients who were supported with the Berlin Heart, 49 (49/82 = 59.76%) weighed

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**Table 1.** Demographic and outcome data for all 36 patients weighing less than 5 kg at the time of ventricular assist device insertion, as well as these same data stratified by diagnostic category

| | All patients | Acquired heart disease | Congenital heart disease |
|---|---|---|---|
| Number of patients | 36 | 8 | 28 |
| BiVAD | 12 | 8 | 4 |
| LVAD | 1 | 0 | 1 |
| sVAD | 23 | 0 | 23 |
| Stroke on VAD | 15 | 3 | 12 |
| Bleeding on VAD | 9 | 2 | 7 |
| Underwent heart transplant | 26 | 8 | 18 |
| Death while on VAD | 10 | 0 | 10 |
| Death after heart transplant | 4 | 1 | 3 |
| Death prior to hospital discharge from hospitalisation for VAD insertion | 11 | 0 | 11 |
| Death after hospital discharge from hospitalisation for VAD insertion | 3 | 1 | 2 |
| Death after cardiac transplantation but prior to hospital discharge from hospitalisation for VAD insertion | 1 | 0 | 1 |
| Alive at time of manuscript submission | 22 | 7 | 15 |
| Dead at time of manuscript submission | 14 | 1 | 13 |

BiVAD = biventricular assist device; LVAD = left ventricular assist device; sVAD = single ventricle-ventricular assist device; VAD = ventricular assist device.

<10 kg at the time of ventricular assist device insertion, and 36 (36/82 = 43.90%) weighed <5 kg at the time of ventricular assist device insertion. This analysis will report the patient characteristics and outcomes of these 36 consecutive children <5 kg who were supported with the Berlin Heart ventricular assist device (age [days]: mean ± standard deviation = 55.9 ± 51.4, median = 35, range = 4–215; weight [kg]: mean ± standard deviation = 3.7 ± 0.69, median = 3.6, range = 2.4–4.9), with the first patient cannulated on October 19, 2009, and the most recent patient cannulated on November 1, 2021. Eight patients with acquired heart disease and biventricular circulation were supported with 8 biventricular assist devices. Five patients with CHD and biventricular circulation were supported with 4 biventricular assist devices and 1 left ventricular assist device, while 23 patients with functionally univentricular circulation were supported with single ventricle-ventricular assist device. Table 1 documents demographic and outcome data for all 36 patients, as well as these same data stratified by acquired heart disease versus CHD.

For the overall population of 36 patients, 72.2% (n = 26) underwent heart transplantation (one of whom required subsequent biventricular assist device support 615 days after initial transplantation, followed by a second cardiac transplant 13 days later [as discussed in detail in the Patients and Methods section of this paper]) and 27.8% (n = 10) died on ventricular assist device. Duration of ventricular assist device support [days]: mean ± standard deviation = 119 ± 81.0, median = 109, range = 4–305. Cumulative days supported with ventricular assist device in all 36 patients was 4296 days (11.76 years). Figure 1 documents longitudinal Kaplan-Meier survival after ventricular assist device insertion with 95% confidence intervals for all 36 patients with a 1-year survival estimate after ventricular assist device insertion of 62.7% (95% confidence interval = 48.5–81.2%) and a 5-year survival estimate after ventricular assist device insertion of 58.5% (95% confidence interval = 43.8–78.3%).

Eight patients with acquired heart disease were supported with 8 biventricular assist devices (age [days]: mean ± standard deviation = 67.4 ± 24.0, median = 74.5, range = 27–90; weight [kg]: mean ± standard deviation = 4.2 ± 0.67, median = 4.2, range = 3.11–4.9). All eight acquired heart disease patients (100%) underwent heart transplantation, and zero died on ventricular assist device. In 8 acquired heart disease patients, duration of ventricular assist device support was [days]: mean ± standard deviation = 51.1 ± 38.0, median = 50, range = 9–130. Cumulative days supported with ventricular assist device in 8 patients with acquired heart disease was 409 days (1.15 years).

Twenty-eight patients with CHD were supported with 23 single ventricle-ventricular assist devices, 4 biventricular assist devices, and 1 left ventricular assist device (age [days]: mean ± standard deviation = 52.6 ± 56.7, median = 31, range = 4–215; weight [kg]: mean ± standard deviation = 3.6 ± 0.65, median = 3.4, range = 2.4–4.9). Of 28 CHD patients, 64.3% (n = 18) underwent transplantation, and 35.7% (n = 10) died on ventricular assist device. Duration of ventricular assist device support was [days]: mean ± standard deviation = 139 ± 79.7, median = 136, range = 4–305. Cumulative days supported with ventricular assist device in 28 patients with congenital heart disease was 3887 days (10.6 years).

Figure 2 documents longitudinal Kaplan-Meier survival after ventricular assist device insertion with 95% confidence intervals for all 36 patients, stratified by diagnostic category (CHD versus acquired heart disease). One-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease patients and 55.6% (95% confidence interval = 39.5–78.2%) in CHD patients, P = 0.036. Five-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease patients and 48.6% (95% confidence interval = 31.6–74.8%) in CHD patients, P = 0.014.

Stroke occurred while on ventricular assist device support in 15/36 patients. None of these reported strokes were life-threatening or necessitated ventricular assist device removal, and some of these strokes were not associated with any long-term neurological deficits. Of 3/8 acquired heart disease patients who had a stroke while on ventricular assist device, all underwent subsequent cardiac transplantation, and zero died while on ventricular assist device. Of 12/28 CHD patients who had a stroke while on ventricular assist device, 8 underwent subsequent cardiac transplantation, and 4 died while on ventricular assist device. In patients who experienced stroke, both bivalirudin and dipyridamole were stopped following diagnosis. CT was then repeated 3 days after the stroke, and if no evidence of bleeding or progression of the stroke was documented, bivalirudin was restarted with an initial partial thromboplastin time goal of 50–70 seconds. CT was repeated again 5 days after the stroke, and if no evidence of bleeding or progression of the stroke was documented, dipyridamole was restarted.

Bleeding complications while on ventricular assist device occurred in 9/36 patients. Of 2/8 acquired heart disease patients who had bleeding complications while on ventricular assist device,

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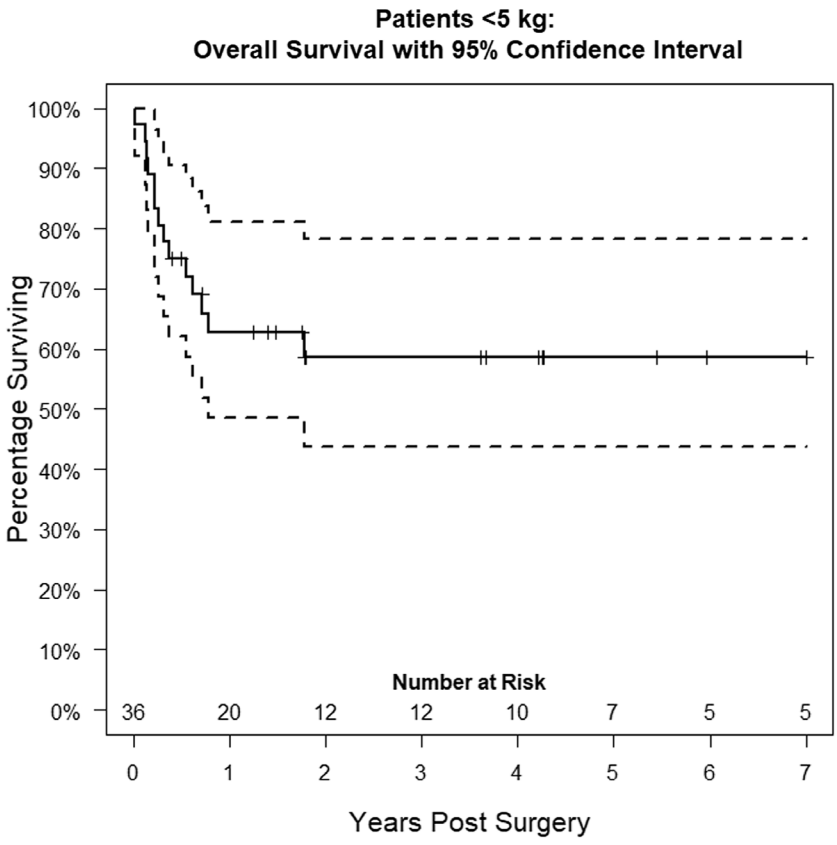


**Figure 1.** This figure documents longitudinal Kaplan-Meier survival after ventricular assist device insertion with 95% confidence intervals for all 36 patients who weighed less than 5 kg at the time of ventricular assist device insertion, with a 1-year survival estimate after ventricular assist device insertion of 62.7% (95% confidence interval = 48.5–81.2%) and a 5-year survival estimate after ventricular assist device insertion of 58.5% (95% confidence interval = 43.8–78.3%).

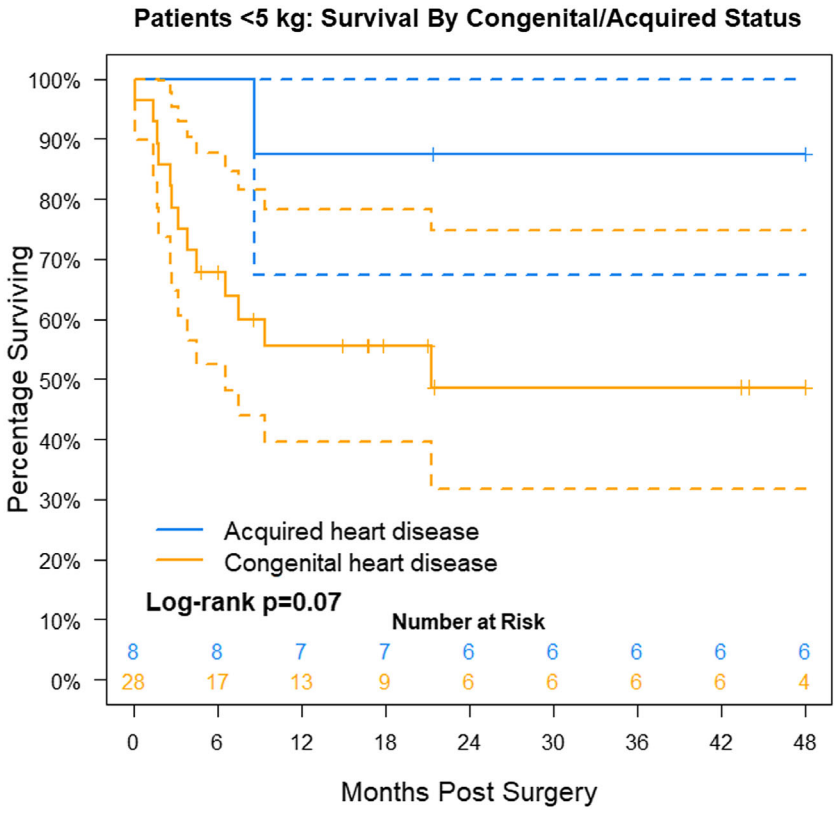


**Figure 2.** This figure documents longitudinal Kaplan-Meier survival after ventricular assist device insertion with 95% confidence intervals for all 36 patients who weighed less than 5 kg at the time of ventricular assist device insertion, stratified by diagnostic category, and reveals better survival after ventricular assist device insertion in acquired heart disease patients. One-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease patients and 55.6% (95% confidence interval = 39.5–78.2%) in CHD patients, P = 0.036. Five-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease patients and 48.6% (95% confidence interval = 31.6–74.8%) in CHD patients, P = 0.014.

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all underwent subsequent cardiac transplantation, and 0 died while on ventricular assist device. Of 7/28 CHD patients who had bleeding complications while on ventricular assist device, 1 underwent subsequent cardiac transplantation, and 6 died while on ventricular assist device.

## Discussion

Our single-institutional analysis of 36 neonates and infants weighing <5 kg at the time of Berlin Heart pulsatile ventricular assist device insertion, comparing those with acquired versus congenital heart disease, reveals three key findings:

1. Small patients <5 kg can be successfully supported with the Berlin Heart paracorporeal ventricular assist device to achieve overall longitudinal Kaplan-Meier estimates for survival after ventricular assist device insertion of 62.7% (95% confidence interval = 48.5–81.2%) at 1 year and 58.5% (95% confidence interval = 43.8–78.3%) at 5 years.

2. Survival in patients <5 kg with acquired heart disease supported with pulsatile ventricular assist device is excellent.

3. Survival in patients <5 kg with CHD is less than in those with acquired heart disease: One-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease patients and 55.6% (95% confidence interval = 39.5–78.2%) in CHD patients, P = 0.036. Five-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in acquired heart disease patients and 48.6% (95% confidence interval = 31.6–74.8%) in CHD patients, P = 0.014.

Clearly, pulsatile ventricular assist device facilitates bridge to transplantation in neonates and infants <5 kg; however, survival after ventricular assist device insertion is less in patients with CHD than in patients with acquired heart disease. Nevertheless, our analysis demonstrates that high-risk patients <5 kg with CHD can be successfully stabilised with pulsatile ventricular assist device insertion while awaiting transplantation. These patients may be extubated, enterally nourished, and optimised for transplantation while on ventricular assist device. In our analysis, CHD patients supported with ventricular assist device had a mean duration of ventricular assist device support that was 88 days longer than that of acquired heart disease patients, a finding likely related to their smaller size, younger age, and longer period of time waiting for a suitable donor heart.

In paediatric patients supported with ventricular assist device, low weight has been consistently cited as a significant risk factor for mortality.[3,13] Specifically, Fouilloux and colleagues[13] found that weight <5 kg was the only independent risk factor for mortality among other factors in a multivariate analysis using Cox regression. In their analysis, Fouilloux and colleagues[13] conducted a retrospective observational study of 54 children (<18 years) supported with a Berlin Heart ventricular assist device across three French institutions between January 2005 and October 2017. Median age at ventricular assist device implantation was 17 (range 2–180) months, and median weight of all patients was 9.8 (range 3.2–60) kg. Only 5 (5/54 = 9%) patients <5 kg were supported, and 3 of these patients (3/5 = 60%) died on ventricular assist device support. Additionally, only 3 (3/54 = 6%) patients in their overall cohort had CHD, meaning 94% of patients had acquired heart disease. Mean length of ventricular assist device support was 62.5 days (range = 5–267) per patient. Survival on ventricular assist device support for the cohort was 73%. Our experience with 36 children <5 kg supported with the Berlin Heart ventricular assist device included a higher percentage of patients with CHD at 77.8% (n = 28), and patients were supported with ventricular assist device for a longer duration (duration [days]: mean ± standard deviation = 119 ± 81.0, median = 109, range = 4–305); yet, our 1-year survival estimate was 62.7% (95% confidence interval = 48.5–81.2%) and our 5-year survival estimate was 58.5% (95% confidence interval = 43.8–78.3%). When considering these small patients <5 kg with acquired heart disease, survival was excellent with a 1-year survival estimate of 87.5% (95% confidence interval = 67.3–99.9%) and a 5-year survival estimate of 87.5% (95% confidence interval = 67.3–99.9%). These survival estimates through 5 years in patients <5 kg are higher than the reported ventricular assist device survival rate (73%) in the French series, which included mostly acquired heart disease patients (94% of the entire cohort). Despite the significant risk associated with low weight, our current protocols for ventricular assist device support successfully mitigate this risk associated with bridging small patients with acquired heart disease to cardiac transplantation.

Although weight <5 kg was the only variable in multivariate analysis to be associated with mortality during ventricular assist device support in the study by Fouilloux and colleagues,[13] other groups have identified additional risk factors for mortality in paediatric ventricular assist device support,[2,3] including the presence of CHD.[6,7] In fact, in a cohort of 97 children <10 kg supported with the Berlin Heart ventricular assist device, pre-existing CHD was one of two factors in multivariate analysis to be associated with mortality (odds ratio = 4.8; 95% confidence interval = 1.5–15.0; P = 0.007); the other risk factor was elevated bilirubin (odds ratio = 5.3; 95% confidence interval = 2.0–14.3; P = 0.001).[6] This multicentre prospective cohort study included all children enrolled in the Berlin Heart US regulatory database between May 2007 and December 2010.[6] Notably, in that analysis, survival for patients <5 kg was poor—most of these patients (63.6%, n = 21/33) died. A subgroup analysis of these patients <5 kg revealed that the presence of CHD was an important univariable predictor of death, with only one patient <5 kg with CHD (out of 13 patients; 7.7%) surviving to transplant. Our analysis reveals that patients <5 kg with CHD may be stabilised with ventricular assist device as a bridge to transplantation with a 1-year survival estimate of 55.6% (95% confidence interval = 39.5–78.2%) and a 5-year survival estimate of 48.6% (95% confidence interval = 31.6–74.8%). However, survival is lower in these patients than in patients with acquired heart disease.

More broadly, the presence of CHD is not only a risk factor for paediatric ventricular assist device support but has also been consistently cited as a risk factor for mortality in paediatric cardiac transplantation.[4,8,11] This concept is particularly relevant as 72.22% (26/36) of patients in our series were successfully bridged to cardiac transplantation. O'Connor and colleagues[8] evaluated preoperative risk factors for mortality in 74 paediatric patients (<21 years) undergoing cardiac transplantation at a single institution from 2010 through 2016. Cohort mean age was 8.8 ± 6.6 years, and the most common indication for transplantation was CHD (48.6%, n = 36). Patient weight was not provided in this analysis; however, only 15 patients (20.3%) were neonates or infants. Overall mortality was 18.9% (n = 14); early deaths accounted for 10 of these 14 deaths (71.4%). In univariable analysis, CHD (versus cardiomyopathy) was a risk factor for early mortality within 30 days or during the initial postoperative admission (odds ratio = 5.14; 95% confidence interval = 1.01–26; P = 0.048), as was functionally univentricular physiology (odds ratio = 4.16; 95% confidence interval = 0.98–17.7; P = 0.05). When considering risk

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factors for overall mortality, CHD still posed risk although statistical significance was not achieved (hazard ratio = 3.2; 95% confidence interval = 0.98–10.4; P = 0.055). Meanwhile, functionally univentricular physiology (hazard ratio = 3.15; 95% confidence interval = 1.03–9.5; P = 0.042) and the requirement for preoperative biventricular assist device support (hazard ratio = 4.8; 95% confidence interval = 1.05–22.2; P = 0.043) were statistically significant risk factors for overall mortality.

These studies contextualise our results by demonstrating that our cohort represents a very high-risk group with multiple significant risk factors for mortality following both ventricular assist device support and cardiac transplantation, including small size, the presence of CHD (as opposed to acquired heart disease), and functionally univentricular anatomy. In our group of neonates and young infants <5 kg of which 64% (n = 23/36) had functionally univentricular physiology, overall longitudinal Kaplan-Meier estimates for survival after ventricular assist device insertion were 62.7% (95% confidence interval = 48.5–81.2%) at 1 year and 58.5% (95% confidence interval = 43.8–78.3%) at 5 years.

### The value of this analysis

Our study adds to the body of knowledge and the literature by providing additional insight into the complexities and challenges of providing ventricular assist device support to neonates and infants <5 kg with CHD in comparison to providing ventricular assist device support to neonates and infants <5 kg with acquired heart disease. We previously reported an analysis of neonates and infants <5 kg supported with ventricular assist device, comparing those with functionally univentricular circulation to those with biventricular circulation, and we concluded that "Pulsatile VAD facilitates bridge to transplantation in neonates and infants weighing <5 kg; however, survival after VAD insertion in these small patients is less in those with univentricular circulation in comparison to those with biventricular circulation."[23] Our current analysis complements this prior study by reanalysing this previously published dataset and comparing patients with CHD to those with acquired heart disease. This overall detailed comparison has not been published until this current manuscript. Our rationale for this approach is that this manuscript allows for a complete assessment and analysis of our comprehensive approach to the management of these challenging patients <5 kg, as well as a comparison of the characteristics and outcomes of those patients <5 kg with CHD to the characteristics and outcomes of those patients <5 kg with acquired heart disease. Our current study highlights the excellent survival that can be achieved in these small patients with acquired heart disease, despite other series highlighting weight <5 kg as a significant risk factor for mortality in paediatric ventricular assist device support. Additionally, survival of patients <5 kg with CHD supported with ventricular assist device is novel with high mortality reported in the literature—the survival estimates reported in our study for these patients represent a vast improvement from previous series. Our finding that CHD patients supported with ventricular assist device have lower survival than their counterparts with acquired heart disease corroborates the literature and adds particularly to the knowledge base for neonates and infants <5 kg. Furthermore, our findings are consistent with the findings of a 2019 publication from the multi-institutional Berlin Heart EXCOR prospective registry that "investigated whether the survival of children weighing <10 kg supported with the EXCOR assist device has improved in recent years and sought to determine the risk factors for mortality."[10] This multi-institutional analysis concluded that "Paediatric EXCOR ventricular assist device therapy has significantly improved for patients weighing <10 kg. Withholding a ventricular assist device is not justified on the basis of the body weight alone." Our current study augments these multi-institutional findings by providing additional data related to small patients with CHD, especially those with functionally univentricular circulation.

Our ultimate goal is to improve the strategies and techniques of ventricular assist device support so that the outcomes of patients with CHD, including those with functionally univentricular circulation, are as good as those achieved in patients with acquired heart disease. We will only achieve this goal by closely examining characteristics and outcomes of all subgroups: CHD, acquired heart disease, univentricular circulation, and biventricular circulation. Some of the risks present in those with CHD are also present in those with univentricular circulation, and each subgroup also has unique risks. This analysis increases our understanding of these risks, with the hope of eventually developing strategies to mitigate these risks.

### Limitations

This analysis is based on our single-institutional experience and the available data in our database. Potential limitations include patient selection bias, institutional bias, confounding bias, and potentially under-powering of the analysis due to the small sample size. Additional follow-up is required on all surviving patients. Further patient accrual will enhance the continued analysis of outcomes. We plan to continue gathering data to provide additional insight as to guideposts for patient selection and predictors of outcomes. It is our hope that by sharing our experience, other hospitals and patients may benefit.

## Conclusions

Pulsatile ventricular assist device facilitates bridge to transplantation in neonates and infants weighing <5 kg; however, survival after ventricular assist device insertion in these small patients is less in those with CHD compared to those with acquired heart disease. One-year survival after ventricular assist device insertion was 87.5% (95% confidence interval = 67.3–99.9%) in patients with acquired heart disease and 55.6% (95% confidence interval = 39.5–78.2%) in patients with congenital heart disease, P = 0.036. Five-year survival after ventricular assist device insertion was 48.6% (95% confidence interval = 31.6–74.8%) in patients with acquired heart disease and 87.5% (95% confidence interval = 67.3–99.9%) in patients with congenital heart disease, P = 0.014. Nevertheless, high-risk patients with CHD can be successfully stabilised with pulsatile ventricular assist device insertion while awaiting transplantation; these patients may be extubated, enterally nourished, and optimised for transplantation while on ventricular assist device.

Our analysis confirms that pulsatile ventricular assist device facilitates bridge to transplantation in neonates and infants weighing <5 kg. Although survival after ventricular assist device insertion in these small patients is less in those with CHD in comparison to those with acquired heart disease, our institutional rates of survival reported in this manuscript for neonates and infants <5 kg with CHD are higher than has been previously reported in the literature. Our institutional survival estimates are promising yet highlight the capacity for improving the outcomes of small neonates and infants with CHD. This differential rate of

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survival between neonates and infants with CHD and those with acquired heart disease represents an opportunity for future research and improvement, with the goal of achieving survival in patients with CHD supported with ventricular assist device equivalent to the survival achieved in patients with acquired heart disease supported with ventricular assist device.

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