Incremental Reduction in the Incidence of Stroke in Children Supported With the Berlin EXCOR Ventricular Assist Device

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Background. Cerebrovascular events (CVEs) are common among children supported with the Berlin EXCOR (Berlin Heart GmbH, Berlin, Germany) ventricular assist device (VAD). Given the high incidence of CVEs associated with this device, we sought to describe our institutional experience in incrementally reducing CVEs in children supported with the Berlin EXCOR VAD.

Methods. We collected pertinent data on 39 consecutive patients who underwent Berlin EXCOR VAD implantation at a single center. Frequency of CVEs was described in risk per implantation, per day, and in reference to the time of therapeutic anticoagulation. Risk factors were analyzed for association with CVEs.

Results. Of the initial 39 Berlin EXCOR VAD implantations, 16 CVEs occurred in 12 patients. The incidence of CVEs decreased with institutional experience per patient ($R^2 = 0.6909$, $p = 0.007$) and per patient-day ($R^2 = 0.8051$, $p = 0.002$). CVEs occurred more frequently before therapeutic anticoagulation targets were achieved (4.1%/day) compared with after therapeutic anticoagulation targets were achieved (0.9%/day; $p = 0.044$).

Conclusions. Incidence of CVEs decreased with institutional experience. The risk of CVE is highest in the immediate postoperative period before therapeutic anticoagulation is achieved. Further studies are warranted in pediatric patients supported with the Berlin EXCOR VAD to confirm our findings in a larger cohort.

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Pediatric patients with decompensated heart failure awaiting heart transplantation frequently require mechanical circulatory support (MCS) in the form of extracorporeal membrane oxygenation (ECMO) for short-term support or ventricular assist devices (VADs) for long-term cardiac support [1]. The past decade has seen a paradigm shift in MCS strategy, especially for providing long-term MCS among pediatric patients. The recent availability and increasing use of the Berlin Heart EXCOR Pediatric Ventricular Assist Device (Berlin Heart GmbH, Berlin, Germany)—a miniaturized VAD that can be implanted in infants and young children—has progressively replaced earlier strategies of using ECMO for providing long-term MCS in children. The use of VADs in children has decreased the transplant waiting list mortality rate and has also helped avoid complications associated with using ECMO to provide long-term support in children [2–5].

However, despite a decrease in cardiac transplant waiting list deaths with the use of MCS, cerebrovascular events (CVEs) continue to remain a significant cause of morbidity for children receiving MCS support. The incidence of stroke across most centers has ranged from 6% to 62% in prior single-center reports [4–8]. Given the varying incidence of CVEs associated with this device, we sought to describe our institutional experience in incrementally reducing CVEs among children supported with the Berlin EXCOR VAD.

Patients and Methods

The University of Arkansas Medical Sciences Institutional Review Board approved this study.

Study Population

This single-center retrospective study reviewed the medical records of 39 consecutive pediatric patients supported with the Berlin EXCOR VAD at our center from 2005 to 2012. This represented 1,533 days of mechanical cardiac support. Pertinent medical information was extracted from the physical and electronic medical records.

Abbreviations and Acronyms

ACA	=	anterior cerebral artery
aPTT	=	activated partial thromboplastin time
BSID-III	=	Bayley Scales of Infant Development—Third Edition
CPR	=	cardiopulmonary resuscitation
CT	=	computed tomography
CTA	=	computed tomography angiography
CVE	=	cerebrovascular event
eCPR	=	extracorporeal cardiopulmonary resuscitation
LVAD	=	left ventricular assist device
MCA	=	middle cerebral artery
MCS	=	mechanical circulatory support
PCA	=	posterior cerebral artery
RICA	=	right internal carotid artery
VAD	=	ventricular assist device
WISC-IV	=	Wechsler Intelligence Scale for Children—Fourth Edition

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Clinical Decision Making for Initiating VAD Support

Berlin EXCOR VAD implantation was considered in patients with decompensated heart failure who were candidates for cardiac transplant and required MCS due to end-organ dysfunction.

Anticoagulation Regimen and Monitoring

After VAD implantation, hemostasis was established during the first 24 hours without anticoagulants. Heparin infusion was started 24 hours after the operation and titrated, with eventual transition to low-molecular-weight heparin (enoxaparin) or warfarin, and anticoagulant management was as previously described [4]. Antiplatelet therapies were initiated and titrated using thromboelastography-based platelet mapping, as detailed previously [4].

Initial monitoring of anticoagulation involved daily prothrombin time, international normalized ratios, thromboelastography, fibrinogen levels, unfractionated/low-molecular-weight heparin anti-Xa levels (depending on the heparinoid used), and platelet counts. While an arterial catheter was available, no heparin was used in the transduction fluids. Activated partial thromboplastin times (aPTTs) were obtained every 6 hours while the patient was maintained on unfractionated heparin. Once antiplatelet therapy was considered, daily thromboelastogram platelet mapping was obtained. Laboratory monitoring was weaned as clinically indicated, depending on the modality and stability of anticoagulation dosage and variables.

Variables and Definitions

Anthropometric and demographic data, preimplantation cardiac diagnosis, ECMO use, cardiac arrest before mechanical support, need for extracorporeal cardiopulmonary resuscitation, need for left VAD (LVAD) vs biventricular assist device, infectious complication while receiving VAD support, and duration of VAD support were tabulated. An infectious complication was defined as positive bacterial culture result associated with a suspicion of infection. An aPTT of 60 seconds was used as the threshold for defining therapeutic anticoagulation with unfractionated heparin in these patients. CVE was defined as a newly diagnosed change in neurologic examination associated with a radiographic change by computed tomogram relative to a baseline computed tomogram before implantation. Neurologic follow-up was described as the Pediatric Stroke Outcome Measure at 60 days and clinical follow-up at 1 year, with appropriate cognitive scales used when available [9].

Statistical Analysis

Anthropometric data, risk factors, and outcomes after explantation were tabulated and compared between patients with and without CVEs using the Student t test, logistic regression, and the Fisher exact test, as appropriate. The α level was adjusted with the Bonferroni correction given the multiple hypotheses tested. Linear regression analysis was performed to evaluate CVE incidence by total events per patient per year, and total events per patient day supported per year. Statistical significance was set at a p value of less than 0.05 for regression analysis. The Fisher exact test was used to compare proportion of days with CVE before an aPTT of 60 seconds was reached compared with after an aPTT of 60 seconds was reached. Statistical significance was set at a p value of less than 0.05. All statistical analyses were performed in StatPlus Mac 2009 software (AnalystSoft, Alexandria, VA).

Results

Patient Characteristics

Patient characteristics and characteristics according to the presence or absence of CVEs are summarized in Table 1. CVEs occurred more frequently in patients supported with a VAD for a longer duration ($p = 0.002$) and less frequently overall in patients who received CPR before mechanical cardiac support ($p = 0.013$) and those receiving LVAD support only ($p = 0.018$). However, once α was placed under the Bonferroni correction ($\alpha = 0.005$), longer VAD support duration was the only statistically significant risk factor for CVE. Neither the use of extracorporeal cardiopulmonary resuscitation ($p = 0.645$) nor the size of the LVAD pump that was used ($p = 0.562$) altered the likelihood of stroke. There was a trend towards more frequent CVEs in patients with culture-positive documented infections during their VAD support ($p = 0.075$) and fewer CVEs in patients who underwent ECMO ($p = 0.076$), although neither of these differences reached statistical significance.

Clinical outcomes in the cohort are presented in Table 2. There was no difference in outcome of device therapy, patient survival, graft survival, or postexplant hospital length of stay whether a CVE occurred. Clinical details of the CVEs are summarized in Table 3. Overall, 12 of 39 patients (30.8%) sustained 16 CVEs: 12 embolic events, 2 hemorrhagic events, and 2 embolic events with simultaneous subdural hematomas. The clinical