VAD as Bridge to Recovery in Anthracycline-Induced Cardiomyopathy and HHV6 Myocarditis

abstract

This report describes an 8-year-old child with acute anthracycline-induced cardiomyopathy triggered by human herpesvirus 6 and the subsequent implantation of an intracorporeal continuous-flow left ventricular assist device (LVAD) and the process to discharge the child from the hospital. After barely 3 months on mechanical support, the device was explanted after thorough examination. Experiences regarding LVAD removal are limited, and no guidelines for echocardiographic and hemodynamic criteria for LVAD removal in children have been published thus far. We present our institutional algorithm for device selection, surveillance in an ambulatory setting, and testing for myocardial recovery, as well as our criteria for LVAD explantation in children. Pediatrics 2014;134:e894–e899

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KEY WORDS assist device, cardiomyopathy, congestive heart failure

ABBREVIATIONS

BSA—body surface area
CMF—cardiomyopathy
EF—ejection fraction
HHV6—human herpesvirus 6
LVAD—left ventricular assist device

Drs Cavigelli-Brunner and Schweiger conceptualized and designed the study, drafted the initial manuscript, and were involved in the direct care of the patient described; Dr Knirsch drafted the initial manuscript and supervised and critically reviewed the manuscript; Dr Stiasny reviewed and revised the manuscript and was involved in the direct care of the patient described; Dr Klingel critically reviewed and revised the manuscript; Drs Kretschmar and Hübler supervised and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Experiences with intracorporeal left ventricular assist devices (LVADs) in children suffering from anthracycline-induced cardiomyopathy (CMP) with subsequent myocardial recovery and LVAD explantation are rare. Protocols for device selection, home discharge, outpatient monitoring, and adequate evaluation for myocardial recovery and decision algorithms for device explantation are missing or have to be generated for this specific patient group.

We describe the use of an intracorporeal continuous-flow LVAD in a child with acute heart failure due to anthracycline-induced CMP triggered by human herpesvirus 6 (HHV6), her subsequent discharge home, and successful device explantation after 149 days on support.

CASE REPORT

An 8-year-old girl (body weight: 25 kg; body surface area [BSA]: 0.97 m²) was admitted to our hospital due to severe, rapid-onset heart failure. Seven months before, she had been diagnosed with a bone sarcoma of the left tibia and was treated by surgical resection and chemotherapy according to the EURAMOS-1 Trial (The European and American Osteosarcoma Study Group), including methotrexate, cisplatin and doxorubicin (cumulative doses: 450 mg/m²). Ten days after the last chemotherapy course, her general condition worsened, and echocardiography showed a dilated left ventricle, a biventricular reduced contractility with an ejection fraction (EF) of 25%, and a shortening fraction of 15%. Despite maximal inotropic support and mechanical ventilation, the patient’s condition deteriorated, and an LVAD implantation with the use of an LVAD HeartWare Ventricular Assist System (HeartWare Inc, Framingham, MA) was successfully performed (Fig 1).

Apart from prolonged medical support, right ventricular treatment requiring initial inhaled nitric oxide until the sixth postoperative day, and milrinone for the first 2 weeks, the patient’s further postoperative course was uneventful. Ventilation time was 7 days, and her ICU stay was 28 days. The child was discharged from the hospital 90 days after LVAD implantation on an oral medication regimen with diuretics, angiotensin-converting enzyme inhibitors, and β-blocking agents and a triple anticoagulation regimen consisting of phenprocoumon, acetylsalicylic acid, and dipyridamole. The assist device was set on a rotation of 2100 rates per minutes. Before discharge, extensive training in handling the LVAD and especially how to react in an emergency situation were provided to the child, her parents, the family practitioner, the whole school class (including teaching staff), and the local emergency providers. The girl lives 1 hour by car from the hospital.

Follow-up at home was uneventful; the patient’s functional status improved; and she attended public school. No significant problems or alarms from the device occurred. Outpatient visits every second week showed improvement in the cardiac function on echocardiography, and brain natriuretic protein levels dropped continuously (maximum: 52 900 ng/L; minimum: 2100 ng/L). Repeated echocardiography under reduced pump flow and finally off-pump found no significant impairment in myocardial function or dilation of the ventricles. Four months after implantation, cardiac catheterization with complete hemodynamic evaluation was scheduled.

Hemodynamic

To achieve appropriate anticoagulation for the off-pump trial, additional intravenous heparin was administered. Under general anesthesia, stepwise reduction of the LVAD was performed until a brief full stop for 10 minutes. During full stop of an LVAD, a significant backflow up to 2 L/min via the outflow graft can occur, similar to severe acute aortic valve regurgitation with the potential risks of acute left ventricular dilation and systemic hypotension due to low cardiac output. This action may distort the results and can lead to an underestimation of the real left ventricular function. Therefore, we temporarily blocked the outflow graft of the HeartWare device by using a 13-mm low pressure Tyshak balloon catheter (NuMED Canada Inc, Cornwall, Ontario, Canada).
ON, Canada) (Fig 2). In addition to a moderate increase in mean pulmonary artery and capillary wedge pressures, the other hemodynamic parameters (ie, cardiac index, pulmonary and systemic vascular resistance, central venous oxygen saturation) remained completely stable. We simultaneously performed an echocardiography, which showed good biventricular contractility with no signs of ventricular dilation. The details of the hemodynamic evaluation are given in Table 1.

### Histologic, Immunohistologic, and Molecular Pathologic Findings

The histopathologic and immunohistologic findings in the heart tissue before LVAD implantation and in the endomyocardial biopsy specimens 4 months after onset of severe congestive heart failure are depicted in Fig 3. All myocardial biopsy specimens were taken from the right ventricle (the first biopsy specimens during surgery for LVAD HeartWare implantation and the second biopsy specimens during cardiac catheterization for hemodynamic evaluation). In the first endomyocardial biopsy specimen, moderate chronic myocarditis in association with a cardiac reactivation of the HHV6 infection was noted. In parallel, we observed anthracycline-induced toxic damage of myocytes and severe interstitial fibrosis. Four months after LVAD implantation, a significant decline in inflammation and elimination of HHV6 genomes, as well as a partial recovery of the myocyte damage and interstitial fibrosis, was demonstrated.

### Explantation of LVAD HeartWare and Follow-up

Clinical, laboratory, echocardiographic, hemodynamic, and histologic evaluations indicated potential myocardial recovery. Because no pediatric weaning criteria have yet been published, we modified the criteria of Dandel et al for the adult population as an approach for the pediatric age group (Table 2). The results indicate promising myocardial recovery, even though not all items of the pediatric modification of the criteria of Dandel et al were fulfilled. The fact that some authors report a time frame of 40 to 80 days for myocardial remodeling when the left ventricle is unloaded also strengthened our decision to explant the device. Successful surgical device explanation via a median re-sternotomy was performed 149 days after LVAD implantation. The insertion spot for the LVAD in the left ventricular apex was closed by using direct sutures. The patient’s postoperative course was uneventful. The child was discharged from the hospital 2 weeks after LVAD explantation on her previous oral anticoagulant regimen and acetylsalicylic acid for anticoagulation. Echocardiography before discharge and during the 4-month follow-up showed a globally reduced biventricular function (left ventricular shortening fraction of 28%, left ventricular EF of 45%), with no valve

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**FIGURE 2**
Cardiac catheterization showing the outflow graft of the HeartWare device blocked by a 13-mm Tyshak balloon catheter on lateral view.

**TABLE 1**
Hemodynamic and Echocardiographic Data Show the Effect of Stepwise Flow Reduction Until Temporary Full Stop of LVAD HeartWare

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Full Flow (2080 rpm)</th>
<th>Reduced Flow (1800 rpm)</th>
<th>Stop Flow (0 rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (l/min·m⁻²)</td>
<td>3.9</td>
<td>5.4</td>
<td>4.26</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>19</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure, mm Hg</td>
<td>11</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, units*m²</td>
<td>1.9</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Systemic vascular resistance, units*m²</td>
<td>12.2</td>
<td>10.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>83</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Arterial blood pressure, systolic/diastolic, mm Hg</td>
<td>70/55</td>
<td>90/50</td>
<td>80/40</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension, mm</td>
<td>37</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Central venous oxygen saturation, %</td>
<td>76</td>
<td>83</td>
<td>77</td>
</tr>
</tbody>
</table>
regurgitation or signs of pulmonary hypertension.

DISCUSSION

We report a case of the first successful temporary use of an intracorporeal LVAD HeartWare device in an 8-year-old girl suffering from anthracycline-induced CMP and details of device explantation. Anthracycline-induced CMP carries a high risk for severe congestive heart failure with irreversible myocardial damage.7 Although CMP can still occur at lower doses, the risk of CMP increases significantly at cumulative doses >550 mg/m².7,8 Combination therapy with other cardiotoxic antitumor drugs and age (young and old) are additional risk factors.8 The prognosis is poor, with up to 50% mortality in 1 year. No effective curative treatment is presently available. Myocardial recovery might still be feasible, but the time period for this ranges from 135 days up to >16 months.3-5,9 Interestingly, in our case, the immunosuppressive activity of anthracycline was found to induce an intramyocardial HHV6 reactivation with inflammation that spontaneously resolved during LVAD treatment. In addition, myocyte damage and interstitial fibrosis showed a partial recovery. These factors could also be due to the known phenomena of reverse remodeling.10 HHV6 is clearly active in pediatric patients with cancer11 and has frequently been detected in explanted hearts from children with dilative CMP,12 even though the clinical significance of these results are unknown. Nevertheless, data on long-term outcomes of patients bridged to recovery versus bridged to heart transplantation are not completely clear in the adult population and are missing in the pediatric population.13

In patients suffering from anthracycline-induced CMP with severe heart failure, long-term mechanical support might become necessary. Based on our experience, to improve quality of life for the child and the whole family, we would recommend the implantation of an intracorporeal LVAD in children with a BSA >0.6 m² and preserved right ventricular function.14 This action potentially allows discharging the child from the hospital to bridge myocardial failure to recovery or to heart transplantation. Initial experience with this device has been promising, with low mortality and complication rates.14-18 Before discharge from the hospital, extensive training for the child, parents, neighbors, local emergency providers, and school staff needs to be instituted. Guidelines for echocardiographic and hemodynamic criteria for LVAD removal in children have not yet been published. In contrast, in the adult population, more differentiated approaches regarding successfully weaning, with repeated
echocardiography, have been published by Dandel et al.\textsuperscript{5,10} To evaluate cardiac recovery under continuous axial flow pumps, a “3-step” approach (regular echocardiography, cardiopulmonary exercise testing, and right heart catheterization) has been established.\textsuperscript{20} Nevertheless, it should be noted that these criteria have not yet been established for congenital heart diseases.

Once in outpatient treatment, frequent and regular ambulant visits, including physical examination, electrocardiography, and echocardiography, are necessary to assess pump settings and predictors for recovery. Thus far, no standardized protocols for the evaluation of myocardial recovery in children on LVADs have been published. Our institutional approach schedules an echocardiography twice a month, with special attention to the following signs of myocardial recovery: increase in EF, normalization of the chamber dimensions, and no relevant valve regurgitation. If these echocardiographic parameters normalize and remain stable under full pump assistance, further evaluation (clinically and echocardiographically) with reduced pump flow (lowest possible pump speed of 1800 rpm and optimal anticoagulation) and finally off-pump testing under hemodynamic monitoring are performed. As a next step, complete invasive hemodynamic and echocardiographic evaluation is recommended with complete pump stop and temporary catheter blocking of the outflow graft of the device to impede retrograde backflow to the left ventricle. This procedure was first described in an adult patient, and we adopted it to our pediatric patient.\textsuperscript{21} For the final decision to explant the device, weaning criteria are still lacking and must be determined for children. We adapted the proposed main weaning criteria for adults by Dandel et al\textsuperscript{5} to our young patient (Table 2).

The present case report reflects our limited experience in weaning a child from an LVAD. Implantation or explantation of an LVAD should be managed carefully. If any doubts exist about myocardial recovery, in the absence of a reason for rapid explantation, further investigations should be performed, and the explantation postponed. Furthermore, as reported for the adult population,\textsuperscript{22} the role of a specific pharmacologic regimen in children cannot be answered with our limited experience. Nevertheless, future prospective clinical trials are needed to validate explantation criteria for the pediatric population.

**CONCLUSIONS**

Third-generation LVADs are safely applicable as intracorporeal devices in children with a BSA ≥0.6 m\textsuperscript{2} and may be used as a bridge to decision. Regular outpatient monitoring and evaluation for myocardial recovery are crucial, because in selected patients, LVAD explantation may become an option with satisfactory outcome.

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**TABLE 2** Established Weaning Criteria for Successful Explantation of Ventricular Assist Devices and Modified Weaning Criteria Adapted for Pediatric Patients and Data of Our Patient

<table>
<thead>
<tr>
<th>Test</th>
<th>Dandel et al\textsuperscript{5}</th>
<th>Pediatric Modification</th>
<th>Our Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiography</td>
<td>Sinus rhythm</td>
<td>Sinus rhythm</td>
<td>Sinus rhythm</td>
</tr>
<tr>
<td>HR &lt; 90 beats per minute</td>
<td>&lt;10 y: HR &lt; 110 beats per minute</td>
<td>15% HR increase during off-pump trials</td>
<td></td>
</tr>
<tr>
<td>No more than 25% HR increase during off-pump trials</td>
<td>No more than 25% HR increase during off-pump trials</td>
<td>Mean 53 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Mean ≥ 55 mm Hg</td>
<td>&lt;10 y: mean &gt; 50 mm Hg</td>
<td>LVEDD ≤ score +2</td>
<td>RV diameter 19 mm, z score 0.2</td>
</tr>
<tr>
<td>Blood pressure (brachial artery)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD ≤ 55 mm</td>
<td>LVEDD ≤ score +2</td>
<td>Mitral valve regurgitation grade I, aortic valve regurgitation grade ( \leq ) 1</td>
<td></td>
</tr>
<tr>
<td>LVEF ≥ 45%</td>
<td>LVEF ≤ 45%</td>
<td>Maximal grade II mitral and/or aortic valve regurgitation</td>
<td></td>
</tr>
<tr>
<td>Maximal grade II tricuspid or pulmonary valve regurgitation</td>
<td>Maximal grade II tricuspid or pulmonary valve regurgitation</td>
<td>Tricuspid valve regurgitation grade I, pulmonary valve regurgitation grade 0</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Cardiac index &gt; 2.6 L/min/m\textsuperscript{2}</td>
<td>Cardiac index &gt; 2.6 L/min/m\textsuperscript{2}</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure (mean)</td>
<td>≤ 13 mm Hg</td>
<td>Pulmonary artery wedge pressure (mean)</td>
<td>19 mm Hg</td>
</tr>
<tr>
<td>Right atrial pressure (mean) ≤ 10 mm Hg</td>
<td></td>
<td>Right atrial pressure (mean) ≤ 10 mm Hg</td>
<td>10 mm Hg</td>
</tr>
</tbody>
</table>

HR, heart rate; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RV, right ventricular; RVOT, right ventricular outflow tract.

\( \text{z} \) score and short-/long-axis ratio.
REFERENCES


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