Durable Ventricular Assist Device Support for Failing Systemic Morphologic Right Ventricle: Early Results

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Background. The systemic morphologic right ventricle (RV) in congenitally corrected transposition of the great arteries or after atrial switch for transposition of the great arteries is associated with late ventricular failure. Although the role of the left ventricular assist device (LVAD) in supporting the failing LV is established, the indications and outcomes of using LVAD in a systemic RV remain unclear. We assessed the role of a third-generation LVAD for systemic RV support.

Methods. Seven patients (mean age, 36 years) received the HeartWare (HeartWare International Inc, Framingham, MA) VAD for systemic RV failure (congenitally corrected transposition of the great arteries in 1 and after atrial switch in 6). Four patients (57%) had severe subpulmonic LV failure, and aggressive perioperative diuresis with or without hemofiltration was used to off-load the subpulmonic LV. The indications of VAD were (1) bridge to transplant in 3 and (2) bridge to decision for a high transpulmonary gradient in 4. Transplantation outcome was compared with systemic RV failure without VAD bridge in 19 patients (years 1989 to 2013).

Results. Systemic RV support alone was achieved in all patients, with no early deaths (≤30 days). Overall, 6 (86%) returned home, 3 (44%) received a transplant, 2 (28%) died of noncardiac causes, and 2 (28%) continue on VAD support (median support, 232 days). Repeat catheterization (n = 4) showed an improved median transpulmonary gradient in 3 patients (median 18.5 mm Hg pre-VAD vs 8.0 mm Hg post-VAD). Two bridge-to-decision patients received transplants at 640 and 685 days. The stroke rate on VAD support was 43% (2 thromboembolic and 1 hemorrhagic; 3 with satisfactory recovery). De novo aortic regurgitation was 29% (n = 2; 1 valve replacement). All patients (n = 3) survived transplantation (vs 10.5% early mortality without VAD bridge; p = 1.00) and were well at follow-up (range, 53 to 700 days).

Conclusions. The third-generation VAD provides durable support for systemic RV failure as a bridge to transplant and as a strategy to reduce pulmonary vascular resistance. Although concomitant subpulmonic LV failure is common, systemic RV support alone was achieved in all patients.


The main patient groups where the systemic circulation is supplied by a morphologic right ventricle (RV) are those who have had an atrial switch operation for transposition of the great arteries (TGA) and patients with congenitally corrected TGA (ccTGA). The morphologic RV is not designed as a durable support for systemic circulation, and systemic ventricular dysfunction and heart failure become common later in life [1]. The atrial switch operation was introduced in the late 1950s, and it is anticipated that growing numbers of aging survivors will increase the burden of health care in the grown-up congenital heart population.

For patients with end-stage heart failure and a failing systemic RV, cardiac transplantation provides the best long-term outcome. In the face of a declining donor pool, many patients would die on the waiting list [2]. In recent years, use of the left ventricular assist device (LVAD) as a bridge to transplant (BTT) has increased substantially, with durable support from newer-generations of the device [3]. However, the experience of using LVAD for patients with failing systemic RV is largely confined to sporadic case reports [4, 5]. The purpose of this report is to describe our institutional experience in the use of a third-generation LVAD.
LVAD in a series of patients with systemic RV failure as a BTT and also as a strategy to improve patients with high pulmonary vascular resistance (PVR) for transplantation.

Patients and Methods
From October 2010 to April 2014, 7 patients (6 men; mean age, 36 years [range, 26 to 41 years]; 6 post-atrial switch, 1 ccTGA; 6 redo operations) received the HeartWare HVAD (HeartWare International Inc, Framingham, MA), a third-generation LVAD, to support systemic RV failure (Table 1). Preoperative echocardiography confirmed severe systemic RV failure in all patients. Concomitant subpulmonic morphologic LV failure was also present in 6 (86%); impairment was mild to moderate in 1, moderate in 1, and severe in 4 (Table 2). The regional National Health Service Research Ethics Committee waived the need for informed consent.

Indications for VAD Implantation
All patients had severe and deteriorating heart failure symptoms despite optimal medical treatment and various adjunctive procedures that were performed to improve heart failure control (Table 1). Many had pacing strategies, including biventricular pacing, with little symptomatic benefit.

The indications for VAD implantation were divided into two groups: (1) 3 patients who were too unwell to wait for a donor (BTT) and (2) 4 patients in whom immediate listing was not possible (bridge to decision [BTD]) due to a high transpulmonary gradient (TPG) and a VAD was implanted as a strategy to improve PVR for transplantation. In addition, 3 of the 4 BTD patients also had prohibitive panel reactive antibody (Table 1). No patients were ventilated pre-VAD but the BTT patients were more unwell and in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class II (all on inotropes) compared with the BTD patients who were in INTERMACS class IV (none on inotropes). The plan in group BTD was to repeat the catheterization to reassess PVR once the systemic output had been optimized using the LVAD for at least 3 months.

Indication for Concomitant Valve Operation
All patients (except 1 with a prosthetic tricuspid valve replacement) had at least moderate (2 severe) systemic atrioventricular valve (AVV) regurgitation, but the systemic AVV was not routinely repaired or replaced concomitantly during VAD insertion. Systemic AVV operations were only undertaken if the patient was deemed to be potentially recoverable from mechanical support (in 1 patient who presented with acute postpartum...
decompensation). No patient had more than mild aortic regurgitation before VAD, and therefore, none required concomitant aortic valve replacement.

Preoperative Optimization of Subpulmonic Ventricle

As per institutional policy, all patients with biventricular failure would receive aggressive dehydration with diuretics with or without combination inotropic therapy (most commonly milrinone) prior to VAD implantation. We aimed to achieve a target central venous pressure (CVP) of less than 10 mm Hg [6]. If necessary, further elective continuous venovenous hemofiltration was used (in 2 patients with severe subpulmonic impairment) [6]. Our goal was to unload and optimize the subpulmonic ventricle to achieve mechanical circulatory support for systemic ventricle alone.

Operative Techniques

Cardiopulmonary bypass was instituted with cooling to 32°C. Bicaval cannulation was preferred and mandatory in the presence of atrial baffle. Superior vena cava and pulmonary artery cannulation were used in 1 patient with an occluded inferior vena cava. Device implantation was performed on a beating heart or with the aid of fibrillation. Cardioplegia arrest was used when a concomitant systemic AVV operation was required. The device was inserted to the inferior (diaphragmatic) surface of the morphologic RV free wall (Figs 1, 2). To achieve an unobstructed inflow:

1. Optimal positioning of the inflow cannula was achieved by using intraoperative transesophageal echocardiography to assist in selecting the optimal device implantation site. This was best achieved when the heart was still full before going on cardiopulmonary bypass. The RV would be indented externally. Transesophageal echocardiography was used to confirm optimal site of implantation and was used again to confirm cannula position after coming off bypass.

2. Careful attention was also paid to resect an adequate amount of coarse muscle trabeculation or muscle bands to prevent obstruction to the inflow cannula. Any obstructive chordae might need to be sacrificed, but papillary muscles were preserved. Because a failing systemic morphologic RV was invariably dilated and assumed a globular shape, a spacer was not typically required.

Strategy for Coming Off Bypass to Support the Subpulmonic Ventricle

The strategy for coming off bypass consisted of a combination of adrenaline, milrinone, and inhaled nitric oxide for subpulmonic ventricular support and vasopressin for systemic vascular resistance control. Noradrenaline was added if vasopressin was insufficient. A pulmonary artery catheter was inserted, where feasible, to guide postoperative management of the inotrope together with echocardiographic evaluation. Because floating of a pulmonary artery catheter would be difficult in patients with
atrial baffles, CVP and echocardiographic evaluation were used instead as guidance.

The inhaled nitric oxide was weaned off first, followed by the vasoconstrictors. The adrenaline came off next, but the milrinone was kept until an angiotensin-converting enzyme inhibitor could be introduced.

The preoperative strategy of strict fluid balance and targeting single-digit CVP was continued after VAD implantation, with aggressive diuresis and hemofiltration if necessary.

**HeartWare HVAD Setup**

The pump is started at 1,800 rpm after coming off bypass for 2 to 3 seconds, allowing hemodynamics to normalize before starting the VAD. The speed is increased gradually until the septum is in the midline, usually at about 2,400 to 2,500 rpm, using transesophageal echocardiography to assess the septum. A flow of 4.0 to 4.5 L/min is adequate for most patients and can usually be achieved at 2,400 to 2,500 rpm and with a mean arterial pressure of 60 to 70 mm Hg. The CVP is kept at less than 10 mm Hg.

**Postoperative Anticoagulation Protocol**

A baseline thromboelastogram was checked preoperatively. No anticoagulation was given within the first 24 hours after the operation. When surgical bleeding subsided (<1 mL/kg/h for 3 consecutive hours), a heparin infusion was started at 1,000 U/h and titrated accordingly to achieve an activated partial thromboplastin time of 60 to 80 seconds (or activated clotting time of 180 to 220 seconds). Aspirin (75 mg daily) was commenced on postoperative day 2 and increased to 75 mg twice daily if the platelet count exceeded 100 x 10^9/L on postoperative day 3. A check thromboelastogram for platelet mapping was repeated on postoperative day 5. If aspirin...
resistance was demonstrated (defined < 50% inhibition), an alternative antiplatelet agent, such as clopidogrel, was started.

Once the patient was stable, without significant hepatic dysfunction or potential for postoperative bleeding, and with good nutrition, warfarin was commenced with a target international normalized ratio of 2.7 (range, 2.0 to 3.0). The heparin infusion was stopped once the international normalized ratio exceeded 2.4. After discharge, subcutaneous tinzaparin (175 U/kg) was used for a subtherapeutic international normalized ratio of less than 2.0, and the warfarin dose was escalated.

**Statistical Analysis**

Statistical analyses were performed using SPSS 20.0 software (IBM Corp, Armonk, NY) at a significance level of 5% (two-tailed p value). Nonparametric univariate analyses were performed using the Mann-Whitney test or the Fisher exact test where appropriate. Survival analysis was performed using the Kaplan-Meier method, and differences between groups were compared using the Mantel-Cox log-rank test.

Outcome measures were (1) early death after device implantation (<30 days), (2) long-term survival and neurologic outcome on HVAD support, and (3) survival outcome after transplant. Outcomes on HVAD were compared with 22 consecutive adult patients with dilated cardiomyopathy (DCM) supported with an HVAD between 2011 and 2012. Survival after transplant was compared with 19 systemic RV failure patients without a VAD bridge who received transplants in our institution between April 1989 and January 2013; of whom, 18 received a heart allograft (5 cCTGA, 13 after atrial switch) and 1 underwent a heart-lung transplant for TGA-ventricular septal defect with Eisenmenger syndrome.

**Results**

Overall, 6 patients (86%) were discharged home, 3 (44%) received a transplant, and 2 (28%) died of a noncardiac cause (Fig 3). The most recent 2 patients (28%) are currently still on VAD support and are waiting for a transplant from home (median support, 232 days; range, 30 to 685 days). VAD support for the systemic ventricle alone was achieved in all patients, with no early deaths (<30 days).

**In-Hospital Outcome**

One BTT patient, who had good recovery from VAD implantation, died in-hospital of a complication after a vocal cord injection (day 62). This patient had persistent bleeding related to the vocal cord injection, which was complicated by septic shock and multiorgan failure.

No patient required mediastinal reexploration for bleeding. Five patients underwent postoperative continuous venovenous hemofiltration: 2 as a strategy to optimize subpulmonic ventricular function and 3 for acute kidney injury. Six patients (86%) were discharged home. The median intensive care unit stay was 6 days (range, 3 to 10 days) and the hospital stay was 28 days (range, 20 to 64 days).

**Outcome After Hospital Discharge**

Six patients (86%) reported symptomatic improvement. In group BTD (n = 4), 2 received a transplant at days 640 and 685, 1 is still on VAD support, and 1 died of sepsis on day 232. This patient required open reduction for a fractured radius after a fall at 3 months post-VAD and sustained a cerebrovascular accident 5 days later. He was readmitted 7 months post-VAD and died of sepsis and renal failure. The origin of sepsis was unclear and did not appear to be related to the VAD. In group BTT, 1 patient received a transplant on day 313, and 1 is still on VAD.

![Flowchart showing outcomes for the 7 patients overall and for the patients with bridge to transplantation (BTT) or bridge to decision (BTD) who were supported with the HeartWare Ventricular Assist Device (HVAD; HeartWare International Inc, Framingham, MA). (INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; RV = right ventricle; TGA = transposition of the great arteries; VAD = ventricular assist device.)](image.png)
A cerebrovascular event occurred in 3 patients (43%), at 3, 4, and 15 months after implantation: 2 were thromboembolic strokes and 1 was an intracranial hemorrhage that required evacuation of the hematoma and shunt insertion. One patient had a mild residual hemiplegia and 2 had complete neurologic recovery. One patient had recurrent episodes of gastrointestinal bleeding. A driveline infection developed in 1 patient that was treated with antibiotics. One patient had recurrent VAD thrombosis, which required thrombolysis and eventually required device replacement at 453 days post-VAD through a left thoracotomy.

Follow-Up Echocardiography, TPG, and Functional Status

Repeat catheterization was available in 4 patients who were discharged home except for the last 2 patients who are still waiting for reassessment. Three of the 4 patients showed improved TPG (median, 18.5 mm Hg pre-VAD vs 8.0 mm Hg post-VAD; Fig 4). The patient who had deteriorating TPG did not acquire symptomatic improvement on VAD (16 mm Hg pre-VAD vs 24 mm Hg post-VAD). The reason for the elevation was unclear, and sildenafil was used to further improve pulmonary hypertension.

Five patients (71%) had at least moderately impaired subpulmonic LV function, and 4 (57%) were severely impaired (Table 2). Two patients (29%) had progressive de novo aortic regurgitation post-VAD (Table 2). One (patient C) had symptomatic deterioration and also borderline TPG (13 mm Hg at 10 months post-VAD vs 23 mm Hg pre-VAD). Sildenafil was used, and tissue aortic valve replacement was also performed at 10 months post-VAD. The TPG dropped to 6 mm Hg on repeat catheterization measurement at 2 months post-AVR (ie, 12 months post-VAD). Three patients had worsening systemic AVV regurgitation post-VAD but did not require reintervention.

Outcome Compared With DCM Patients Supported on HVAD

Early mortality was 4.5% (1 of 22) in the DCM group vs 0% in the systemic RV group ($p = 1.00$), and the cerebrovascular event rate was 23% (5 of 22) vs 43% in the systemic RV group ($p = 0.33$). Kaplan-Meier analysis showed survival of 91% at 6 months and 86% at 1 year in the DCM group vs 83% at 6 months and 63% at 1 year in those with systemic RV failure on HVAD ($p = 0.38$ by log-rank; Fig 5).

**Outcome of Transplant Compared With Systemic RV Failure Without VAD Bridge**

The 3 patients with VAD bridge survived transplantation vs 10% early mortality (2 of 19) without VAD bridge ($p = 1.00$). One required posttransplant extracorporeal membrane oxygenation support and 1 required hemofiltration for renal support. All 3 patients were still alive and well on follow-up at 2, 13, and 23 months after transplant.

**Comment**

Our report shows that the third-generation continuous-flow LVAD technology can be used to provide durable support for systemic RV failure as a BTT and as a strategy to reduce PVR. The BTT patients were sicker on inotrope therapy in INTERMACS class II compared with BTD patients who were not on inotrope therapy in INTERMACS class IV. Although this is the largest series of systemic RV failure patients supported on VAD in the literature, this represents an early and evolving experience of a limited number of patients. Nonetheless, outcome in this difficult group of patients has been acceptable compared with our experience in the non-congenital population supported on the HVAD for LV failure.

Our report serves to highlight several important points. More than half of the patients also had severe subpulmonic LV impairment, but systemic VAD support alone was achieved in all patients [7]. Therefore, measures to optimize the subpulmonic ventricle are
essential preoperatively and postoperatively and include aggressive preoperative and postoperative volume off-loading with diuretics (with or without hemofiltration), strategy for coming off bypass to support the subpulmonary ventricle, and maintenance of optimal heart failure medications upon hospital discharge. We also postulate that a morphologic LV ventricle in the subpulmonic ventricle is more durable and reduces the need of subpulmonic ventricular support. In our pediatric experience using Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany), the need of biventricular support was much higher and was required in approximately half of the patients. Whether this difference could be due to the use of newer generation and continuous-flow device is conjectural.

After HVAD implantation, ventricular function did not necessarily improve, and reason for this is unclear. However, an improvement of heart failure status in the absence of marked changes of LV or RV function post-VAD had also been reported in our larger group of noncongenital patients supported with the HVAD [8].

AVV regurgitation is also present preoperatively in most patients with systemic RV failure. The indication of adjunctive systemic AVV replacement remains debatable, and we only intervene if the patient is deemed recoverable. Furthermore, some of the chordae had to be sacrificed (but papillary muscles were preserved in all cases) to provide an unobstructed VAD inflow, and worsening of systemic AVV regurgitation was therefore observed in some patients postoperatively. Although systemic AVV competency is not required for the function of a continuous-flow LVAD, it is not known whether more aggressive strategy to replace AVV will provide complete left atrial unloading, expedite the reduction of TPG, and therefore result in a better long-term outcome.

Device implantation in a morphologic RV is reportedly more challenging, but the difficulties of cannula placement could not be overrated [9, 10]. The systemic morphologic RV invariably assumes a globular shape when it fails and loses its tripartite structure, which then allows a relatively straightforward positioning of the cannula. The surgical challenges are mainly related to multiple previous operations and their sequelae. These occur in the form of adhesions and anatomic abnormalities of the systemic and pulmonary venous baffles. Excluding any interatrial and inteventricular communication is imperative. Because the morphologic RV is invariably dilated and has lost its tripartite morphology, this is also perhaps why problems with VAD flow and arrhythmia are not any higher in our experience compared with the noncongenital population.

Competency of the aortic valve, unlike the systemic AVV, is required for adequate functioning of VAD flow. When to replace the aortic valve during VAD implantation is an area of great controversy [11]. After LVAD implantation, a continuous, nonpulsatile flow leads to chronic strain on the aortic valve, leading to its dysfunction and de novo aortic regurgitation was observed in 2 of our 7 patients (29%). This seemingly high incidence of de novo aortic regurgitation may be an incidental finding in a small cohort, but whether a conotruncal anomaly, such as TGA, is more susceptible to the chronic strain from continuous device flow is a subject for further investigation. A dilated aortic root and ascending aorta, which may lead to a dysfunctional aortic valve, is a known phenomenon in conotruncal defects [12]. Furthermore, abnormalities of the aortic media in these conotruncal defects have been found to be qualitatively similar and quantitatively identical to Marfan syndrome [13]. A leaking aortic valve without intervention will increase the loading stress on the systemic RV, and reduction of TPG would not be possible. Therefore, we performed a late operation on the aortic valve in 1 patient and based this mainly on his symptoms and the persistent elevation of pulmonary artery pressure at repeat catheterization. We continued to observe until transplantation another patient with moderate aortic regurgitation who demonstrated improved pulmonary artery pressures.

There were other important lessons, and these relate mainly to the risk of thromboembolic complications. Thromboembolic stroke occurred in 2 patients, including 1 who had an additional problem with recurrent device thrombosis. When device thrombosis occurs, our first-line treatment for those with intracorporeal device is thrombolysis. Nevertheless, repeated episode of clots in this patient led to device change, which was approached through a left thoracotomy. It is unclear whether risk of clot formation is higher in a device implanted in a morphologic RV than in an LV due to its geometric difference and heavy trabeculation with more turbulent flow. There was also a trend for a higher stroke rate compared to the DCM group, although all patients had satisfactory neurologic recovery. In addition, the bleeding risk could not be underestimated because hemorrhagic stroke developed in 1 patient, and 1 died as a result of bleeding and the complications that ensued after a noncardiac procedure.

In conclusion, our experience shows that the third-generation VAD has provided durable support for failing systemic RV, both as a BTT and as a strategy to reduce secondary pulmonary hypertension to allow patients to undergo transplantation. This represents an early and evolving experience of a limited cohort, but the use of VAD to support systemic RV failure will assume an increasing importance due to an anticipated growing number of these patients in the future. Late effects on the aortic valve remain to be determined.

References


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Mark your calendar for the 51st Annual Meeting of The Society of Thoracic Surgeons (STS) to be held at the San Diego Convention Center in San Diego, California, January 24-28, 2015. The STS Annual Meeting offers you a chance to meet the experts, network with colleagues from around the world, and participate in a dynamic learning experience.

This preeminent educational event is open to all physicians, residents, fellows, research scientists, perfusionists, physician assistants, nurses, and others interested in cardiothoracic surgery.

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An advance program with information about housing and registration was mailed to STS members this fall. Nonmembers may contact the Society to receive a copy of the printed advance program; however, detailed up-to-date meeting information will be available on the STS website at www.sts.org/annualmeeting.

I hope to see you in San Diego.

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