Current Status of Pediatric Ventricular Assist Device Support

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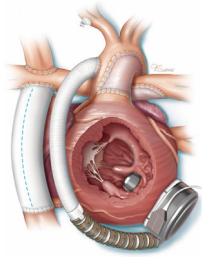
The last decade has witnessed significant advancement in the field of ventricular assist device (VAD) support. Although device options for pediatric patients were previously severely limited because of body size constraints, this frustrating situation has gradually been changing, owing to ongoing device miniaturization. Recognition of the superiority of VAD support compared with conventional extracorporeal membrane oxygenation support has spurred enthusiasm for VAD support in children. In this article, we discuss the current status of pediatric VAD support; where do we stand now and where will we be heading? Because this field is rapidly changing, it is anticipated that this article will provide a general overview of what is currently occurring in the field of pediatric VAD support.
Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 20:2-8

Introduction

There has been substantial advancement over the last decade in the field of pediatric ventricular assist device (VAD) support. Among the many milestones reached in this regard, the successful completion of the Berlin Heart Investigational Device Exemption trial is considered to be one of the most significant.[1] A key finding from this study is the superiority of VAD support over extracorporeal membrane oxygenation (ECMO) in transplant candidates. An improved understanding of VAD support physiology has certainly contributed to the popularization and widespread adoption of pediatric VAD support. In this article, we describe the current status of pediatric VAD support, with a particular focus on how the field has been changing in recent years.



Placement of an implantable continuous-flow device with concomitant Fontan completion.

Central Message

The field of pediatric VADs has continuously been evolving, with a recent trend in the increasing use of temporary devices and implantable continuous-flow devices.

Increasing Use of Temporary Devices

Until recently, ECMO support has been the mainstay of temporary mechanical circulatory support in pediatric heart centers worldwide. This has, however, been changing with the increasing use of temporary VAD support over the last few years.[2] With greater familiarity and confidence with VAD support, pediatric centers now appear to have a lowered threshold to select temporary VAD support over the conventional ECMO. A wider recognition of superiority of VAD

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Dr Adachi serves as a consultant and proctor for Berlin Heart Inc. and HeartWare Inc. and as a consultant for the New England Research Institute, for which Texas Children's Hospital receives a compensatory salary support. Dr Burki has no conflicts of interest to disclose. Dr Fraser served as the principal investigator for the Berlin Heart Investigational Device Exemption Trial. He does not receive personal compensation for this role.
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http://dx.doi.org/10.1053/j.pcsu.2016.09.010

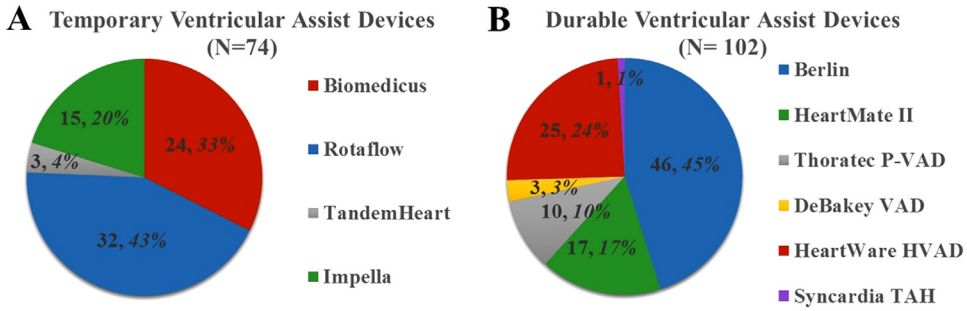

Figure 1 Overall experience of VAD support at Texas Children's Hospital; temporary devices (A) and durable devices (B). (Printed with permission from Texas Children's Hospital.)

support over ECMO is also driving this trend. In general, the temporary VAD system provides better decompression of a failing left ventricle compared with ECMO as the latter positions the inflow cannula in the right side of the heart; hence, decompression of the left heart is indirect.[3] At Texas Children's Hospital (Houston, TX), a total of 74 temporary VADs have been used since 1998 (Figure 1A). The majority (76%; 56 of 74) of these experiences were with extracorporeal centrifugal devices (Biomedicus; Medtronic, Minneapolis, MN, and Rotaflow; MAQUET Cardiovascular, Wayne, NJ) via central cannulation. In our program, however, percutaneously placed temporary VADs (e.g., Tandem Heart; CardiacAssist Technologies, Pittsburgh, PA, and Impella; Abiomed, Inc., Danvers, MA) are being used more often in recent years. Notably, the use of Impella has rapidly increased because of ease of placement and size variations that permit wider application in the pediatric population. These catheter-based percutaneous VADs are limited with respect to flow capability and degree of cardiac decompression compared with a full-flow device such as the Rotaflow pump. Nonetheless, our preliminary experience with the first 15 Impella VAD implants has been promising. Further refinement is required to define the role of these 'partial' flow devices in the armamentarium of the comprehensive pediatric VAD program.

Increasing Use of Continuous-Flow Devices

Another interesting trend in the field of pediatric VAD support is the increasing use of adult continuous-flow devices, such as the HeartMate II (St. Jude Medical, Inc., St. Paul, MN) and HVAD (HeartWare Inc., Framingham, MA). This shift in paradigm is primarily driven by significantly better complication profiles of continuous-flow devices compared with pediatric-specific pulsatile pumps. According to a report by Rossano and associates,[4] approximately half (49%; 45 of 91) of the long-term devices registered in the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) registry are continuous-flow devices. The HeartMate II is an excellent option for adolescents with a body surface area of approximately 1.3 m^2 or larger. With appropriate patient selection and implantation techniques, the outcome of HeartMate II LVAD support in the pediatric population is excellent (>90% bridge to transplant).[5] The use of the HeartMate II has all but eliminated the need for Berlin EXCOR 50 ml and 60 mL pumps in the pediatric population. In our opinion, the most significant influence this device has had on the pediatric community is that pediatric programs have learned how to manage children with an implantable VAD, even as outpatients. This essentially has formed the fundamental basis to move forward to the next stage, which is the use of an implantable continuous-flow device in small children. Owing to its compact design, the HVAD has become the most widely used continuous-flow VAD in children. At the annual meeting of the International Society of Heart and Lung Transplantation in 2016, Conway and associates[6] reported the worldwide experience of HVAD use in the pediatric population. As of June 2016, there have been a total of 171 HVAD implantation at 29 centers across 11 countries (16 in North America, nine in Europe, and four in the rest of the world), with the majority (65%) of implantations performed in the last 2.5 years. At Texas Children's Hospital, we have performed a total of 102 long-term VAD implantations to date, with slightly less than half (44%; 45 of 102) being implantable continuous-flow devices (Figure 1B). In particular, the HVAD has been used most frequently in our program, resulting in 25 implantations, currently representing the largest single-center experience among the pediatric heart centers worldwide according to the manufacturer's registry. In the next section, we discuss what we believe is important in achieving successful continuous-flow VAD support in children.

Adult Devices in Children: What's Important?

Inflow cannula

When implanting adult VADs in children there is an inherent issue related to the 'patient-device' size mismatch. The deleterious impact of the size mismatch on patients' survival has been clearly demonstrated.[7] Unlike the Berlin Heart EXCOR system, which has several different sizes of pumps and cannulas, size mismatch is inevitable if placing adult continuous-flow VADs in small children. Careful

consideration should be given, therefore, to avoid or mitigate issues inherently associated with patient-device size mismatch.

In our opinion, the most crucial aspect is accurate placement of the inflow cannula. Placement of a VAD in a child's relatively small ventricular cavity requires meticulous technical precision. Even in adult patients, VAD support for non-dilated hearts (e.g., restrictive cardiomyopathy) demonstrates limited tolerance for minor technical imperfections.[8] In the interest of avoiding inflow-related issues such as suctioning of the ventricular septum or pump thrombosis, the inflow cannula must be placed paying particular attention to its angle relative to the ventricular septum. Based on extensive experience with the HeartMate II, the axis of the inflow cannula, hence the relationship of the inflow relative to the ventricular septum, appears to play a role in the incidence of pump thrombosis.[9] Arguably, lessons learned from the HeartMate II may not necessarily apply to the HVAD because of differences in device designs. It is our belief, however, that the basic principle of inflow cannula angle relative to the septum should hold true, irrespective of device type. The ideal configuration should be that the axis of the inflow cannula lies in parallel to the septum rather than perpendicularly.

Owing to its unique design whereby the inflow cannula is directly attached to the pump housing, the HVAD pump is placed adjacent to the heart. This feature allows for its pump housing to be placed within the pericardial space. With this standard technique, so-called *intrapericardial placement*, the inflow cannula often lies more or less in a horizontal plane, thereby perpendicularly oriented to the interventricular septum. To ensure a more vertical orientation, we utilize a different approach to HVAD placement. We use the cardiac apex as an insertion point of the inflow cannula (i.e., coring site), consistent with the standard implantation technique. Instead of letting the pump float in the pericardial cavity, however, we affix the pump housing within a small pocket created by dividing the left hemidiaphragm.[10] With this maneuver, the cardiac apex is relocated more medially and caudally; more importantly, the angle of the inflow cannula is actively controlled by the surgeon (Figure 2). As a result, the tip of the inflow cannula sits more vertically, satisfying the requirement that it lie virtually in parallel to the interventricular septum. With a similar concept, Gregoric and colleagues[11] advocate a technique involving insertion of the pump into the diaphragmatic surface of the left ventricle instead of cardiac apex. While their approach is a reasonable option in adult-sized hearts, it does not seem to be a very appealing approach in children. Because of the smaller surface area of the inferior left ventricular wall in children, the posterior descending coronary artery may be distorted or jeopardized by anchoring a sewing ring. It remains to be seen whether or not these extra efforts to align the inflow cannula with the interventricular septum makes any difference clinically. The overall incidence of pump thrombosis in 25 patients with HVAD at Texas Children's Hospital is 0.095 events/patient-year (two events over 21 years of cumulative support). This number seems to be comparable to adult data.[12] Focusing just on small children with a body surface area of $< 1.0\ m^2$, the pump thrombosis rate is 0.135 events/patient-year (one event over 7.4 years of cumulative support in 11 patients [five of them with complex congenital heart disease: two biventricular and three univentricular physiology]) in our experience at Texas Children's Hospital. This incidence appears to be superior to the recently reported data of a multicenter study (0.70 events/patient-year: four events over 5.7 years of cumulative support in 13 patients).[13]

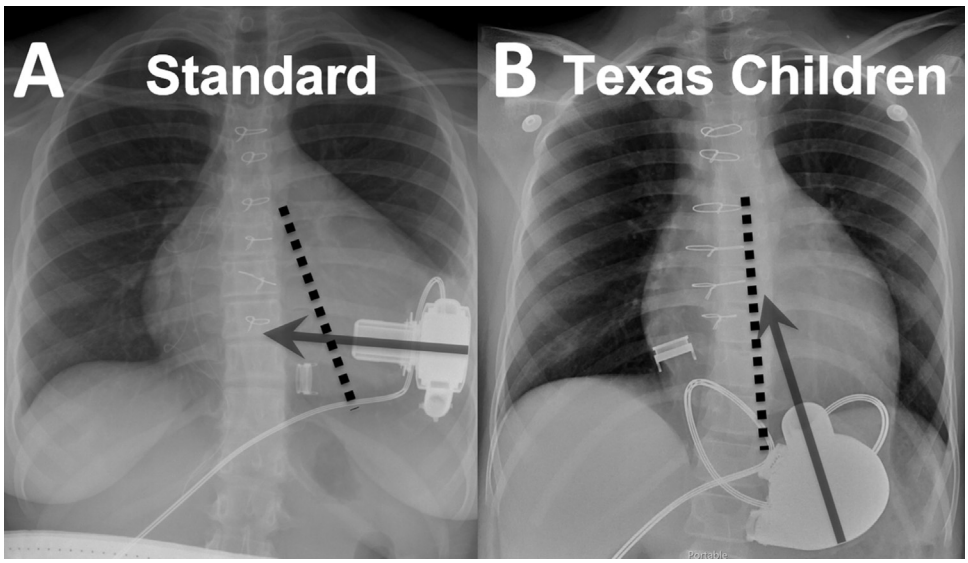

Figure 2 Postoperative chest X-rays with the standard intrapericardial placement (A) and with the Texas Children's modification (B). A dotted line represents an imaginary line of the interventricular septum. With the standard technique, the inflow cannula lies in a horizontal plane, resulting in a rather perpendicular orientation to the septum. With the Texas modification, the inflow cannula sits in a vertical plane and parallel to the septum. (Printed with permission from Texas Children's Hospital.)

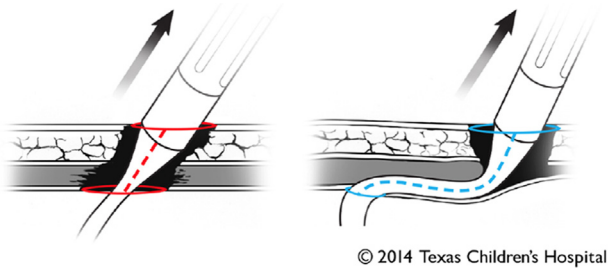

Figure 3 Creation of a large defect in the abdominal wall with the standard tunneling technique (A) and with the Texas Children's modification (B). Note the size difference between the large connector part (approximately 12 mm in diameter) and the cable (4 mm). (Printed with permission from Texas Children's Hospital.)

Driveline

In our opinion, special care also must be taken when tunneling the driveline of implantable VADs through the thin abdominal wall in small children. Goldstein et al[14] reported an interesting observation using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry data. The authors demonstrated that the younger the patient (among adults) the higher the risk of driveline infection. Because of the retrospective nature of registry data, the cause of this finding remains speculative. One may assume that younger patients are physically active, whereby the driveline exit site is subjected to greater traumatic stress, an identified risk factor for developing driveline site infections. In our experience, pediatric patients are prone to driveline site issues due to vigorous physical activity and inattentiveness to the driveline. It is understandable that the risk of developing a driveline complication is reportedly high in children, with up to 80% of VAD-specific infections involving the driveline.[15] The problem with the standard tunneling technique for the HVAD driveline is that the integrity of the abdominal muscle layer, which is the primary supporting mechanism of the driveline, is destroyed by passing the large connector part (12 mm in diameter, triple the diameter of the cable; Figure 3). Surgical modifications such as ours aimed at maintaining the abdominal wall integrity may reduce driveline complications in active children.[16]

What Long-term Support Provides in Children

Timing for activation on the heart transplant waiting list

Through these technical modifications and resultant improvement in outcomes, our confidence in managing patients with implantable VADs as outpatients has bolstered over time. This has prompted several other changes downstream in our clinical practice. The most significant change involves our policy regarding the waiting status on the transplant list after VAD placement. In the past, we used to reactivate the patient soon after VAD placement. Our current practice is that we intentionally keep the patients inactive on the transplant waiting list for at least for 3 months after initiating implantable VAD support. The rationale behind this practice change is that such a 'grace' period affords these patients opportunities for physical and psychological recovery following heart failure exacerbation and the invasive surgery for VAD placement. This strategy has been serving our program well. In fact, most children have shown positive trends in somatic growth and nutritional status during the course of VAD support.[17] Such changes undoubtedly make these patients better candidates for future transplantation. We have, however, quickly realized that the advantage of this approach is not just limited to nutritional rehabilitation, as discussed in the next section.

Myocardial recovery

The most important advantage of our waiting policy is that the grace period provides an opportunity to continually assess for the possibility of cardiac recovery.[18] Cardiac recovery during long-term VAD support is a well-known phenomenon, but one that rarely occurs. According to the INTERMACS data, VAD explantation for cardiac recovery occurs in only approximately 1% of all patients.[19] Pediatric data are even more pessimistic in that the reported rate of cardiac recovery was only 0.6% according to the PediMACS registry.[20] This is despite the commonly held belief that pediatric myocardium possesses greater potential for recovery than the adult myocardium.[21] Given the lack of reliable tests that can be used to accurately predict who may recover and who may not, the only way to confirm irreversibility of myocardial dysfunction would be to provide enough time for potential recovery. Anecdotal experiences[18] suggest that it typically takes at least 2 months for chronically failing hearts to recover. In other words, if patients with VAD are actively listed for heart transplant soon after VAD placement, and then receive transplant relatively quickly (which is often the case in children), clinicians may miss the opportunity for recovery. It is possible that the pediatric community sees cardiac recovery so rarely because transplant occurs too early.

In our program, all patients with HVAD support will be placed under a surveillance protocol for myocardial recovery at hospital discharge. Our surveillance protocol has previously been described.[22] In particular, we place a special emphasis on patients with dilated cardiomyopathy 'without' non-compaction morphology. In our experience, none of the patients with left ventricular non-compaction showed signs of myocardial recovery. Virtually all of the non-compaction patients in our series had endocardial fibroelastosis, which is an indicator for cardiac non-recovery. In other words, if the histology of left ventricular core does not identify such an unfavorable finding in dilated cardiomyopathy patients, we try to maximize the potential for recovery with aggressive pharmacologic support and complete decompression of the failing ventricle. Most of our patients receive beta-blockers, angiotensin-converting enzyme inhibitors, and spironolactone. Dosages of these medications are maximized as clinically tolerated. Another important aspect of clinical management for myocardial recovery is complete decompression of the heart. In the early phase of VAD

support (typically, the first 3 to 6 months), we run the VAD at a relatively high rpm. Adequacy of cardiac decompression is determined by regular echocardiographic assessment. During this decompression phase, we aim for a decrease in size of the left ventricular cavity and intermittent opening of the aortic valve. We also monitor serial changes in brain natriuretic peptide as a marker of ventricular decompression. With adequate decompression, brain natriuretic peptide levels often normalize during this phase. At 3 months of support, if there are early signs of myocardial recovery (i.e., improving left ventricular systolic function), patients remain under the surveillance protocol without activation on the transplant list. If there are no signs of recovery or the underlying conditions are unfavorable for recovery (e.g., complex congenital heart disease), the patients are actively listed at this point. Although we do not have a clear cut-off value for this decision, we utilize a left ventricular ejection fraction of 40% or greater to define 'VAD responder,' as advocated by the Utah group.[23] In our HVAD series, there are 11 patients with a diagnosis of dilated cardiomyopathy supported for over 3 months. Of the 11 patients, four had histological evidence of endocardial fibroelastosis, with (n=3) and without (n=1) non-compaction. In the remaining seven patients, four (57%) had normalization of left ventricular ejection fraction (>60%) during the course of support. Two underwent VAD explantation successfully and the other two are being closely monitored for potential explantation in the near future. This experience may suggest that myocardial recovery with long-term VAD support is a more realistic therapeutic goal than generally believed if candidate selection and clinical management during VAD support are appropriate. More vigorous works would be necessary in both clinical and basic science arenas given the shortage of pediatric-specific data on this particular topic.[21]

Extended support in adolescents

Another novel approach using implantable VAD in the pediatric population is extended support in adolescents. It is known that adolescence carries the worst post-transplant outcomes in any solid organ transplant, including heart transplant.[24] To discuss potential reasons behind such observations is beyond the scope of this article. Nevertheless, this is an important fact of which clinicians must remain cognizant when managing adolescent patients on VAD support as bridge to transplantation. While adolescence is a less than ideal age for transplantation, these patients represent the best candidates for long-term VAD support. Their body size, including cardiac geometry, is nearly adult sized, thereby eliminating the concern for the patient-device size mismatch. Adolescents do not have typical adult comorbidities such as hypertension or diabetes. Considering unfavorable post-transplant outcome in otherwise ideal candidates for long-term VAD support, it may be reasonable to keep such patients on VAD support for extended durations until they outgrow the 'unfavorable' period for transplant. In our program, there have been seven patients with a support duration of more than 1 year, with the longest being 5 years (who is continuing on support). This longest support patient is approaching adulthood, and she will autonomously decide whether she is amenable to a transplant or prefers to continue VAD support indefinitely.

VAD Support for Single Ventricle

Currently, implantable continuous-flow VADs are used mainly for cardiomyopathy in the pediatric population. According to Conway's report on the worldwide experience in the use of HVAD for children, patients with congenital heart disease as underlying conditions comprise only 17% (28 of 171).[6] As the field matures, however, it is expected that the proportion of congenital heart disease will increase. In our experience with the HVAD, 32% (8 of 25) had congenital heart disease, with four of them having single ventricle physiology (two with Glenn and the other two with Fontan circulation at the time of HVAD implant).

Fontan circulation

From the standpoint of VAD support, patients with failing single ventricle certainly comprise the most challenging group because of complex anatomy and physiology. Given the palliative nature of staged single ventricular procedures, pessimism exists that all such patients (including those who have completed Fontan operation) will ultimately fail. Currently, experience in VAD support for single ventricle circulation is limited. In reviewing the outcomes of the Berlin Heart EXCOR in North America, Weinstein and associates[25] found that survival was significantly worse in the single ventricle cohort as compared with those with biventricular physiology (42% *vs* 73%). One of the most interesting observations is significant differences in survival depending on which stage of single ventricle palliations the Berlin Heart EXCOR was implanted. Comparing with the dismal outcome (11% survival) in the Stage I palliation group, survival with VAD support for Stages II (58%) and III (60%) are more favorable. These numbers are in fact superior to what has previously been reported on outcomes of ECMO support for single ventricle physiology (Stage II [41%][26] and Stage III [35%]).[27] The type of VAD (i.e., pulsatile *vs* continuous-flow) also seems to play an important role in patients with single ventricle physiology. Horne et al[28] have described the superiority of continuous-flow VAD over pulsatile VAD in single ventricle physiology. Pulsatile VAD decompresses the failing systemic ventricle only during pump diastole, which is typically only 60% of each pump cycle duration. Theoretically, continuous decompression of the failing ventricle would be advantageous in single ventricle circulation. Because of the lack of a subpulmonary ventricle, the pulmonary circulation is a 'passive' flow. Continuous decompression of the ventricle, hence the pulmonary venous return, enhances the efficiency of such pulmonary circulation (Figure 4). There have been several reports describing successful use of an implantable continuous-flow VAD in larger children with failing Fontan circulation.[29,30]

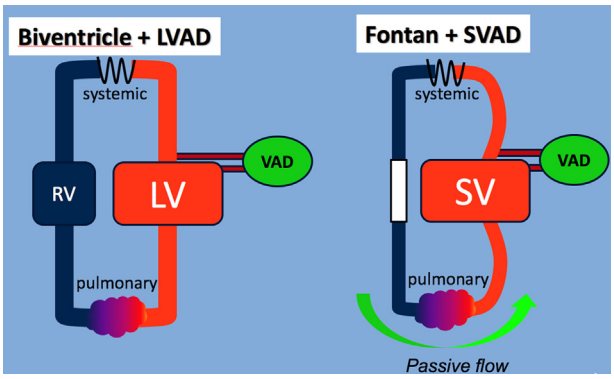

Figure 4 Schematic illustrations of VAD support for biventricular physiology and single ventricle physiology. Because of the lack of subpulmonary ventricle, the pulmonary circulation is a passive flow in single ventricle. (Printed with permission from Texas Children's Hospital.)

As Fontan circulation can fail for multiple reasons, such as systolic or diastolic dysfunction, elevated pulmonary vascular resistance, and a combination of these,[28] careful determination of the exact cause of circulatory failure is necessary. If systolic dysfunction is the predominant cause of circulatory failure, it is likely that VAD support for the failing systemic ventricle would significantly improve hemodynamics.

Glenn circulation

Utility of an implantable continuous-flow VAD in failing Glenn circulation is even more limited. This would certainly reflect the fact that most children with failing Glenn physiology would be too small to accommodate an adult-sized implantable VAD. We expect that with ongoing miniaturization of such devices, implantable continuous-flow VAD will soon become the mainstay of VAD support for failing Glenn physiology. We have experienced one patient at Glenn stage that developed cardiogenic shock while waiting for heart transplantation. The underlying anatomy was consistent with unbalanced right dominant atrioventricular septal defect and

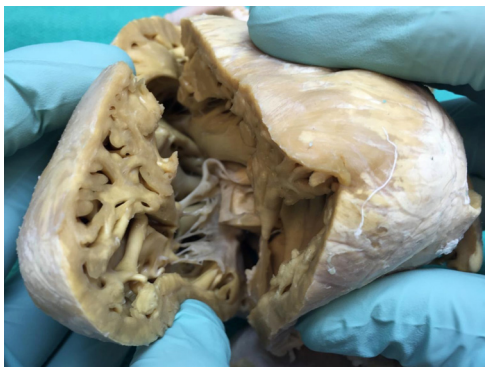

Figure 5 An internal view of a functionally single ventricle heart with right ventricle morphology (right ventricular dominant atrioventricular septal defect). The apical portion of the systemic ventricle contains heavy trabeculations, resulting in limited space for placement of a VAD. (Printed with permission from Texas Children's Hospital.)

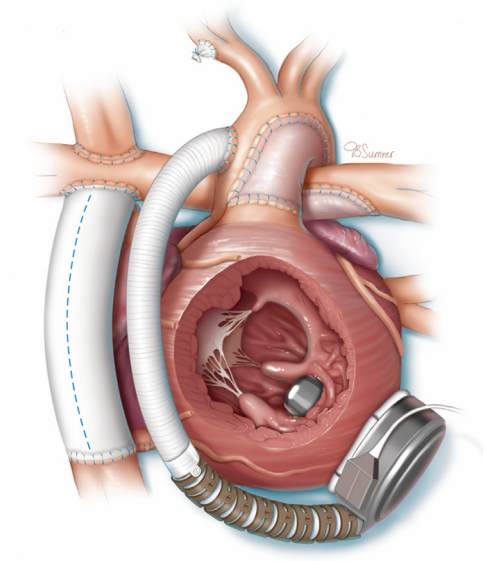

Figure 6 Creation of Fontan circuit concomitant with the placement of the HeartWare HVAD. (Printed with permission from Texas Children's Hospital.)

malposed great arteries in the setting of right atrial isomerism. The patient had previously undergone multiple surgeries, including repair for total anomalous pulmonary venous return, common atrioventricular valve repair, and bilateral bidirectional Glenn shunts.[31] The challenging aspect of VAD support in this type of patients is that the ventricular chamber is not ideal for VAD insertion. Because of right ventricular dominance, the morphologic left ventricle is usually too small for device insertion. At the same time, the right ventricle is not ideal either because of the presence of heavy trabeculations (Figure 5). In this particular case, we elected to place a VAD in the massively dilated common atrium. Although this patient was reasonably well supported and successfully bridged to transplantation, we noticed that her exercise tolerance during VAD support was more limited than typical patients on VAD support, which we attributed to persistent cyanosis. In a subsequent patient with failing Glenn physiology, therefore, we performed Fontan completion concomitantly with HVAD implantation to eliminate the deleterious effect of chronic cyanosis (Figure 6). The patient is now 7 months post implant and has been doing well as an outpatient with normal oxygenation saturation levels while awaiting heart transplant.[32] There are a number of children at the Glenn stage that cannot be progressed to the Fontan completion because of poor ventricular function. Again, the emphasis here is not only bridging such patients to transplant but how to improve their transplant candidacy. The approach described here, i.e., mechanically assisted Fontan completion, is just an example of attempts at improving candidacy. It is anticipated that the pediatric community will continue to strive to establish how we can incorporate VAD support in the current clinical practice. The use of continuous-flow VAD in children, particularly with complex congenital heart disease, has just started and hence is in its early infancy. It remains to be seen how the field matures in the future.

Summary

In the pediatric population, temporary VADs and continuous-flow VADs are gaining widespread acceptance and are being used more commonly. Long-term VAD support not only improves candidacy for transplant but also provides an opportunity to assess for myocardial recovery. Even more extended support may be a valid approach in the adolescent patient given suboptimal post-transplant outcomes in this age group. VAD support for complex congenital heart disease, particularly failing single ventricle physiology, is challenging. Notwithstanding, single ventricle VAD will become a more common practice given the increasing number of such patients.

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