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Review

Left ventricular assist device support as destination therapy in pediatric patients with end-stage heart failure

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ABSTRACT

The development of ventricular assist devices to sustain the circulation represents one of the great achievements in the treatment of heart failure. Though early (1st generation) pulsatile devices required that patients remain hospitalized while on support, newer 2nd and 3rd generation continuous-flow (CF) devices have allowed for hospital discharge, expanding their use beyond bridge to transplantation to include permanent support. This indication, referred to as "destination therapy" is emerging as a viable alternative to heart transplantation in adults, and more recently, children. Though no formal indications exist for destination therapy in children, it may be considered in lieu of transplantation in patients with non-cardiac life-limiting comorbidities, severe pulmonary hypertension, obesity (BMI $>$ 35 kg/m^2), recurrent malignancy, or if it is their preference. One group for whom DT may be most appropriate is those with advanced dystrophinopathies for whom post-transplant outcomes remain poor. Outpatient management of the pediatric destination therapy patient requires close monitoring by a multidisciplinary team of physicians, nurses, pharmacists, social workers, nutritionists, and psychologists. Because destination therapy in children remains quite rare, little is known about long-term outcomes in this population, though studies of children supported as outpatients as a bridge to transplantation suggest that survival is excellent and functional status improves post-implantation. As ventricular assist devices continue to develop, the future will not only include application of this technology to a more diverse group of patients, but the additional challenge of supporting patients for increasingly longer durations, managing late complications, and facilitating improvements in quality of life.

1. Introduction

The pursuit of the artificial heart dates back to at least 1937, when Vladimir Demikhov first used a machine to support the circulation in a dog for over 5 h [1]. In 1952, approximately 15 years after the work of Demikhov, Dr. Forest Dodrill is credited with the first successful mechanical circulatory support in a human [2]. Predating Dr. Christian Barnard's historic first heart transplant in 1967, the original intended use of these devices were for either permanent replacement for the failing heart or temporary surgical support. Since then, with the advent of heart transplant outcomes outpacing those of ventricular assist devices (VADs), there has been a conceptual shift in the utility of VADs to be used primarily as a bridge to transplantation (BTT), rather than as a definitive therapy. In recent years, however, with dramatic advancements in both the longevity and quality of life of VAD patients, we are once again returning to first principles and using mechanical support for long-term purposes. This indication, referred to as "destination therapy" (DT) is emerging as a viable alternative to heart transplantation in adults, and more recently, children. This manuscript describes the contemporary approach to DT in children with advanced heart failure, with specific emphasis on candidate selection, outpatient management, adverse events, and patient outcomes. Perspectives on future directions are also discussed.

2. The Development of DT in Adults With End-stage Heart Failure

The development of VADs to sustain the circulation represents one of the great achievements in the treatment of heart failure, a disease that affects nearly 6 million Americans and carries a poor prognosis even with optimal medical therapy [3]. The landmark 2001 Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study demonstrated both a 48% reduction in all-cause mortality, as well as improved functional status and quality of life in non-transplant eligible patients supported with the HeartMate VE pulsatile left ventricular assist device (LVAD) (Thoratec Corp., Pleasanton, California) versus optimal medical management

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[4,5]. Over time, as a result of accumulated experience as well as ongoing technological improvements, follow up studies of the REMATCH cohort have shown improved survival and an overall reduction in adverse events in LVAD patients compared to those receiving medical therapy alone [6,7]. Similar results were reported in the Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent (INTrEPID) trial, which demonstrated improved 6 and 12 month survival using the Novacor device (World-heart, Oakland, California) in a population nearly identical to that studied in REMATCH [8].

Despite these encouraging results, both the REMATCH and INTrEPID trials were conducted using early pulsatile devices, whose benefits were generally limited to short-term outcomes because of device failure. The development of second-generation axial continuous-flow devices (CF-VADS), including the Jarvik 2000 (Jarvik Inc., New York, New York) and the HeartMate 2 which are smaller, more durable, and quieter than their predecessors, resulted in improved end-organ function, reduced adverse events, and better survival event profile up to 15 months post-implant compared to earlier devices [9–14]. This new potential for long-term survival with acceptable quality of life opened the doors for CF-VADs to be used as DT, and in a direct comparison of CF-VADS to pulsatile VADS, Slaughter et al. showed improved survival, functional status, and quality of life at 2 years for patients in patients ineligible for transplant supported by the HeartMate 2 CF-VAD versus a pulsatile device [15]. Shortly thereafter, the HeartMate 2 received FDA approval for destination use in 2010 [6]. Since then, CF-VAD technology has continued to evolve, with the introduction of 3rd generation devices, such as the HeartWare HVAD (HeartWare Inc., Framingham, Massachusetts) which is even smaller than earlier CF-VADs (Fig. 1). In the third generation devices, bearingless magnetically levitated impellar designs can function for several years with minimal wear and tear [16]. As of 2016, according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), nearly 5000 CF-VADs have been implanted as DT in adults, with 46% of all implantations occurring for this purpose [17].

3. The Emergence of DT as an Option for Children

Heart failure in children is quite rare. For this reason, CF-VAD development has primarily focused on adults. To date, the only FDA approved VAD for children and infants is the EXCOR device (Berlin Heart, Berlin, Germany), a pulsatile, paracorporeal pneumatic pump that obligates inpatient hospitalization until transplant and, thus, is not suitable for DT [18,19]. This restriction, in addition to the much less favorable adverse event profile for the Berlin Heart as compared to CF devices, has motivated the pediatric heart failure community to favor CF devices which now are used increasingly in children as BTT [20]. However, DT remains infrequent with few reports in the literature. As a result, much of what we know about DT in children is extrapolated from the more extensive outpatient CF-VAD BTT experience [21,22] (Table 1). In an early study of adolescents, Cabrera et al. reported that children ages 11–18 years supported with the HeartMate 2 had outcomes similar to adults, though the follow up time was limited to 6 months [23]. More recently, the Heartware HVAD been used successfully in children [24–27]. Over time, as surgical and medical management techniques have improved, implanting centers have been emboldened to attempt implantation in even smaller patients, broadening the population of children for whom outpatient/DT therapy may potentially be available. Implantations in patients with body surface areas as small as 0.7 m^2 have been reported [28]. CF-VAD use has also expanded to include implantation in children with congenital heart disease, including single ventricle lesions, notably those with Fontan physiology [29,30].

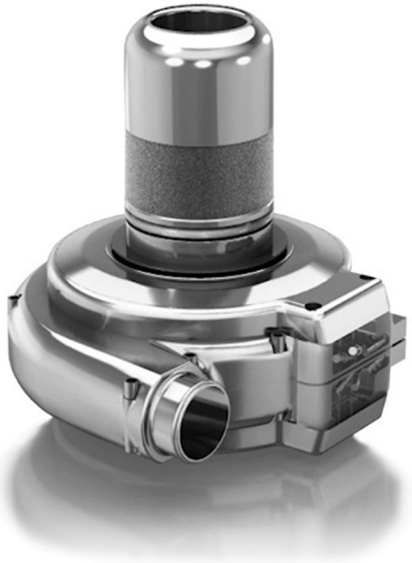

Fig. 1. The HeartWare HVAD. Reproduced with permission of Medtronic, Inc.

One ongoing limitation to our understanding of DT and CF-VAD use in children overall is the relatively few numbers of children implanted at any single center. Fortunately, the development of Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) database in 2012 has allowed for pooling of data among > 35 centers, and has recently published its first series of reports detailing the indications, outcomes, and adverse events of VAD patients < 19 years old, including those with CF devices [28,31,32]. To date, over 400 implantations are registered in PediMACS [32]. Although only 8 implantations were for DT, 45% of children with CF-VADs were discharged from the hospital, a sub-group whose experience is in many ways broadly generalizable to those on destination therapy [28].

4. Management of the DT Patient

Owing to the rarity of DT in pediatrics, the literature provides little to guide the management of these patients. For that reason, what follows relies not only on the limited extant literature but also on our experience at Stanford University, where we have implanted > 35 CF-VADs in children since 2010, including 4 for DT.

4.1. Candidate Selection

Selection of the DT patient is in many ways similar to determining transplant candidacy. Patients must be fully informed as to the responsibilities and lifestyle limitations associated with life on mechanical support (i.e. lifetime anticoagulation, no swimming). The patient's ability to adhere to the treatment regimen should be ascertained prior to implant.

Though no formal indications exist for DT in children, situations in which DT may be appropriate are outlined in Table 2. Reasons for DT include non-cardiac life-limiting comorbidities, severe pulmonary hypertension, obesity (BMI > 35 kg/m^2), recurrent malignancy, or patient preference. One group for whom DT may be most appropriate is those with advanced dystrophinopathies for whom post-transplant outcomes remain poor [33]. Several studies have shown the CF-VAD implantation is possible in this population, including Perri et al., who recently published a report of 7 cases of adolescent and young adults with dystrophinopathies (6 with Duchenne Muscular Dystrophy) who survived a median of 21.7 months post-implant [21,34]. At Stanford, we have implanted CF-VADs in 4 patients with dystrophinopathies, one who survived to transplantation, one of whom died secondary to medication noncompliance, and 2 who are on DT and are still living at 5 and 6 years post-implant. Both of the living patients have required multiple device revisions, including one who underwent HM2 to HVAD conversion in 2016 due to pump thrombosis. Of note, as we have