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HEART FAILURE (HJ EISEN, SECTION EDITOR)

Current Role of the Total Artificial Heart in the Management of Advanced Heart Failure

Nathaniel Melton[1] · Behzad Soleimani[2] · Robert Dowling[2]

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Abstract

The total artificial heart (TAH) is a form of mechanical circulatory support that involves resection of the native ventricles followed by placement of a device that can restore total pulmonary and systemic flow. Given the increasing burden of congestive heart failure and cardiovascular disease, the number of people in need of cardiac replacement therapy will continue to grow. Despite aggressive efforts to expand the donor pool, the number of heart transplants in the United States (US) has plateaued at less than 3000 per year. In addition, there is increasing recognition of the long-term complications of current generation left ventricular assist devices such as progressive aortic insufficiency, complications related to blood trauma, and both early and delayed right ventricular failure. These factors may serve to expand the role of the TAH in the treatment of patients with end-stage heart failure particularly if new generation devices are developed that are durable, have an improved safety profile, and are totally implantable.

Purpose of Review

To review the role and current evidence of the use of the TAH in the management of advanced heart failure and discuss development of recent TAHs that may have an impact on the field in the near future.

Recent Findings

Many patients that receive a heart transplant are bridged with a mechanical support device, most commonly a left ventricular assist device (LVAD). However, there is a small subset of patients with profound biventricular (BV) failure or structural abnormalities that preclude LVAD placement, who will require support with a biventricular assist device (BiVAD) or TAH. There are numerous studies showing the efficacy of the TAH in bridging to transplantation. Also, recent studies have shown equal rates of bridging to transplantation between patients receiving a TAH compared to a BiVAD. However, BiVAD support has a higher incidence of stroke in addition to complications related to the native heart such as arrhythmias and valve dysfunction. Currently, there are multiple new generation artificial hearts in both preclinical development and in clinical trials for both bridge to transplant and destination therapy.

Summary

TAH have been shown to be effective for circulatory support in select patients with end-stage heart failure. Current LVADs are associated with significant long-term complications related to retention of the native heart and pump design. Many of these complications may be addressed by the increased use of cardiac replacement therapy, i.e., total artificial hearts. Multiple generations of both pulsatile and advanced design continuous flow TAH are under development which have the potential to expand the role of TAHs.

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✉ Nathaniel Melton
meltonnl@upmc.edu

Behzad Soleimani
bsoleimani@pennstatehealth.psu.edu

Robert Dowling
rdowling@pennstatehealth.psu.edu

[1] Department of General Surgery, UPMC Pinnacle, Brady Hall, Ninth Floor, 205 South Front Street, Harrisburg, PA 17104, USA

[2] Penn State Heart and Vascular Institute, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA

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Introduction

Adults with advanced heart failure experience symptoms that interfere with daily life and have a limited prognosis [1–3]. Cardiac transplantation remains the treatment of choice for select patients who remain symptomatic despite optimal medical management [2, 3]. However, given the increasing burden of congestive heart failure and cardiovascular disease, the number of people in need of transplants continues to exceed the number of hearts available. The number of transplants performed in the USA has only increased from 2193 in 2006 to 3244 in 2017 [4]. Despite this increase, the number of patients awaiting a heart transplant has increased from 2424 in 2006 to 3623 in 2017 [5]. Additionally, there are many patients who are not deemed suitable for transplant who will benefit from mechanical circulatory support. This discrepancy has led to the significant increase in the use of mechanical circulatory support devices (destination therapy). According to the latest Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report, the number of LVADs placed as destination therapy exceeds the number placed as a bridge to transplant [6]. In 2017, approximately 50% of recipients had some form of a support device prior to transplantation [5].

As a result of the continued discrepancy between the number of patients on the waiting list and available hearts, mechanical circulatory support has emerged as a standard long-term therapy for adult patients with intractable heart failure. This has led to the design of numerous implantable devices to treat advanced heart failure [1, 7, 8•]. From 2006 to 2017, a total of 25,145 of these devices were implanted in the USA [6]. Many of these patients can be supported by left ventricular assist devices (LVAD). However, a subset of these patients have severe biventricular failure (BV) and/or other conditions that would preclude LVAD implantation. In this subset of patients, the TAH may be the better treatment option. This review paper will explore the role of the TAH in the management of advanced heart failure with an emphasis on which patients may benefit either acutely or in the long term from total heart replacement. We will also discuss new devices on the horizon and their potential impact on patient management.

Patient Selection

Left ventricular assist devices are the primary long-term mechanical circulatory support device for patients with advanced congestive heart failure as a bridge to transplantation, destination therapy, or as a bridge to myocardial recovery [3, 5, 6]. Since the milestone REMATCH trial demonstrated clinical success with LVADs as a long-term therapy for end-stage heart failure patients [9], these devices have become more sophisticated and easier to implant [7, 8•]. With the introduction of second-generation continuous flow devices and refinements in surgical techniques, there was considerable optimism that the incidence of both early and late right ventricular failure would no longer be an issue. However, this has not been realized and RV failure remains a major concern after the implantation of an LVAD and is a major cause of early morbidity and mortality [10–13]. Even with the newer, continuous flow, devices, the incidence ranges from 9 to 44% [10, 11, 13]. In addition, according to the latest INTERMACS data, one of the major factors associated with an increased early hazard of mortality after LVAD implantation was RV dysfunction [6].

There have been multiple attempts to identify which patients are likely to suffer from RV failure early after LAVD placement. Fitzpatrick et al. analyzed retrospective outcomes for patients who underwent LVAD placement to determine a risk score for developing post-LVAD right ventricular failure [12]. They found the most significant predictors of right heat failure after LVAD placement to be cardiac index, RV stroke work index, severe preoperative RV dysfunction, creatinine, previous cardiac surgery, and systolic blood pressure. Similarly, Drakos et al. found that preoperative need for intra-aortic balloon counter pulsation, increase pulmonary vascular resistance, and destination therapy were predictive of RV failure post-LVAD [11]. The sheer number of models to predict early RV dysfunction demonstrates both their limited predictive ability and the significance of this problem.

As previously mentioned, RV failure remains a major cause of early post-LVAD morbidity [10–13]. However, late post-LVAD RV failure, defined as needing right ventricular mechanical support, inotropic support, or pulmonary vasodilators more than 14 days after LVAD implantation, is being increasingly recognized as a significant problem. According to the latest INTERMACS data, 2% of patients required RV mechanical support early after LVAD implantation, while 1% required late mechanical support [6]. Two recent studies found the incidence of late RV failure to be 7.3% and 11% [14, 15]. Rame et al. found that late RV failure was associated with significantly more gastrointestinal bleeding, sepsis, and acute renal dysfunction, but there was no difference in 1-year survival [14]. Takeda et al., however, found that late RV failure was associated with a decreased 2-year survival, not during LVAD support, but after transplantation [15].

For patients with biventricular (BV) failure, para-corporeal biventricular assist devices (BiVADs), implantable BiVADs, and TAHs all are options to provide biventricular support. While these devices are associated with different adverse events, there is evidence of improved survival with placement

of a TAH compared to a BiVAD [16]. In addition, the fourth INTERMACS report showed improved survival at 3 and 6 months among patients with BV failure supported with a TAH versus a BiVAD [17]. As the experience with the TAH increases, it continues to gain further acceptance as a therapy for patients with irreversible biventricular failure [7, 8•, 18–20].

Another potential obstacle to long-term success of LVAD support is the development of aortic insufficiency (AI). The etiology of AI is felt to be increased distending forces on the proximal aorta and aortic annulus [21]. There is also evidence to suggest that commissural fusion contributes to development of both aortic stenosis and AI [22]. Significant AI leads to decreased systemic perfusion and subsequent end-organ dysfunction secondary to the recycling of regurgitant flow across the aortic valve [21, 23, 24, 25•]. Overall, significant AI after LVAD implantation is associated with reduced cardiac output, higher LV end-diastolic diameter, higher rates of rehospitalization, and increased mortality [25•].

The development of AI, which was originally observed with first-generation pulsatile devices, is also seen with current continuous flow devices. Aggarwal and colleagues evaluated 79 patients undergoing LVAD implantation with the Heart Mate II (Thoratec Corp, Pleasanton, CA). The incidence of AI in their study was 52%, which was not associated with an increase in mortality. However, they did find the incidence of AI increased over time [24]. This was also shown in a study by Soleimani et al., where freedom from AI was 100% at 6 months and 68.4% at 12 months [26]. The ability to identify patients who require long-term support and are at increased risk of progressive AI may allow for identification of patients who may be better served with removal of the native heart and placement of a TAH.

The TAH has been implanted in patients for a variety of underlying etiologies and INTERMACS profiles of advanced heart failure [27•] (Table 1). As the experience with the TAH continues to expand, patients with conditions, such as irreversible biventricular failure, decompensated right heart failure on LVAD support, and failure to wean from extracorporeal membrane oxygenation (ECMO), should be considered for TAH placement [19, 28, 29] (Table 2). In addition, the TAH is indicated in patients with clinical conditions or anatomical factors that are not suited for LVADs, such as patients with small ventricles (restrictive cardiomyopathies), patients with unfavorable anatomy such as a post-infarction VSD, congenital heart lesions, significant LV thrombus or primary cardiac malignancy [19, 28, 29]. Lastly, cardiac graft failure is the major cause of death among heart transplant recipients [18]. Despite this, only 2% of this population can receive a new heart transplant, largely due to the shortage of donors [18]. The TAH provides an option for these patients [30].

Table 1 Etiology and INTERMACS profile of advanced heart failure in patients receiving a TAH [27]

	TAH patients ($n = 450$) (%)
Etiology	
Dilated cardiomyopathy	225 (50.0)
Restrictive cardiomyopathy	105 (23.3)
Ischemic cardiomyopathy	92 (20.4)
Congenital heart disease	15 (3.3)
Hypertrophic cardiomyopathy	13 (2.9)
INTERMACS profile	
1 (critical cardiogenic shock)	189 (43.1)
2 (progressive decline on inotropes)	163 (37.1)
3 (stable, inotrope dependent)	43 (9.8)
4 (resting symptoms on oral therapy)	32 (7.3)
5–7 (less sick)	12 (2.7)

Table 2 Current clinical indications for TAH implantation

Irreversible, severe biventricular failure
Decompensated right heart failure on LVAD support
Heart allograft failure or rejection
Recurrent/recalcitrant ventricular tachycardia/fibrillation
Intracardiac thrombus or tumor
Post-infarction ventricular septal defect
End-stage congenital heart disease
Aortic insufficiency or other valve issues with left and/or right ventricular failure
Ventricular failure with small ventricles in patients with restrictive cardiomyopathies

Syncardia TAH

Currently, the Syncardia TAH (SynCardia Systems, Inc., Tucson, AZ) (Fig. 1) is the only TAH available for clinical use approved by the FDA. This device is approved as a bridge to transplantation in patients that are at imminent risk of death from biventricular heart failure and are transplant eligible. This TAH is also undergoing clinical trials to be used a destination therapy [31]. One important consideration when evaluating a patient for this device is the patient's chest size. Given that this TAH occupies approximately 400 cc within the chest, patients must have a posterior sternum to anterior spine measurement at the level of the tenth thoracic vertebrae of at least 10 cm. This pulsatile TAH consists of two artificial ventricles, each made of polyurethane housing with polyurethane diaphragms that separates the blood from the air chambers. Each ventricle has an inflow and outflow valve to control the flow of blood through the device and can generate a stroke volume of 70 cc. The ventricles are each connected to the native atria via inflow connectors and the outflow cannulas

Fig. 1 70 cc (left) and 50 cc (right) Syncardia Total Artificial Heart (courtesy of syncardiastage.wpengine.com)

are sewn to the aorta and pulmonary artery. There is a percutaneous pneumatic driveline from each ventricle which is connected to an external console that provides diagnostic and monitoring information. The Freedom Driver, which is a portable, battery powered, lighter pneumatic pump, has recently been approved for use and allows for patients to be discharged from the hospital.

The original Syncardia TAH had a 70 cc stroke volume and was designed to support patients with a body surface area (BSA) of at least 1.7 M^2. Unfortunately, this has limited the use of the device to being implanted into predominately adult males. To increase the number of potential recipients, the smaller 50 cc model was designed and is currently in clinical trials [32]. This model is intended to support patients with a BSA less than 1.85 M^2. This will expand the patient population that has access to TAH support [33].

Outcomes

In the landmark trial that established the TAH as a relevant option as a bridge to transplantation study, 81 patients received a TAH, with 79% surviving to transplantation, and 70% surviving at least 1 ear [20]. One- and five-year survival rates for patients who were successfully bridged to transplant were 86% and 64%, respectively. This study included patients who were eligible for transplantation, had New York Heart Association Stage IV heart failure, and hemodynamic insufficiency. Importantly, all these patients were deemed poor LVAD candidates.

Since this time, there have been numerous studies on patient outcomes using the TAH as a bridge to transplantation. In 2014, Virginia Commonwealth University Medical Center published their experience with the Syncardia TAH [34]. They implanted 66 patients over a span of 6 years. These patients were supported for a mean of 87.5 days. Seventy-six percent were successfully bridged to transplantation, 15% were discharged home on a Freedom Driver, 11% were still waiting transplantation, and 14% died on the device. Copeland et al. had similar data, with 101 patients supported for a mean of 87 days with 68.3% of their patients being successfully bridged to transplantation [35].

The current surgical options for bridge to transplantation therapy in patients with biventricular failure are the TAH or BiVADs. There is scattered data comparing these two treatment modalities. A multicenter French study in 2012 attempted to determine whether bridging with a TAH or BiVAD impacted transplantation rates [16]. They evaluated 383 patients and found no statistically significant difference in rates of bridging to transplantation. However, they did find that significantly higher rate of stroke in patients receiving a BiVAD. Recently, Cheng et al. showed that patients bridged with a TAH had higher post-transplantation rates compared to patients that were bridged with a BiVAD [36]. This differed from Levin et al., who showed similar bridge to transplantation rates and post-transplantation survival rates between patients treated with a BiVAD versus a TAH [37].

Recently, a large multicenter study was done that analyzed data related to survival, adverse events, using competing outcomes from patients who received TAHs from 2006 to 2017 [37]. Using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, 450 patients were evaluated. One of the interesting findings was that 71% of patients in high-volume centers were alive on the TAH or had undergone transplantation at 1 year after implantation versus 57% in low volume centers. This suggests that patient selection, timing of intervention, and device management play a vital role.

Novel TAHs

Although the Syncardia TAH is the only artificial heart available for clinical use in the USA, it is not without its limitations, as it does not fit in many men and most women. The limited durability, percutaneous tubes, and bulky external equipment also limit the quality of life. This has led to the research and design of newer and more novel devices. These devices may address some of the adverse events associated with LVADs and the Syncardia TAH (Table 3). In addition, the shift from volume displacement pumps to continuous-flow devices has progressively decreased size and increased the durability of LVADs. Not surprisingly, the development of continuous-flow TAHs is underway [8•].

Table 3 Adverse events addressed with novel TAHs

Early and late right-sided heart failure
Progressive aortic insufficiency
Ventricular arrhythmias
Blood trauma and subsequent non-surgical bleeding
Need for systemic anticoagulation

BiVACOR (Houston, TX)

The BiVACOR TAH (Fig. 2) is a continuous flow TAH that uses rotary pump technology to provide support. The device consists of a single, magnetically levitated impeller positioned between separate right and left ventricular chambers. On either side of the impeller are blades that simultaneously generate independent flow from each ventricle. A unique feature of this device is that the disk's axial position can change according to the loading conditions, allowing for a Frank-Starling like response [8•, 18, 38].

There are other features of this device that make it unique and potentially advantageous. The expected durability is approximately 10 years, which is attributed to the magnetic levitation and lack of any contacting surfaces. This artificial heart also has a smaller design, so it will accommodate most male and female. Lastly, in pre-clinical implants in a bovine model, the BiVACOR device generated mean flows of 10 L/min, stable left-right balance and increased flow in response to increased metabolic demands [8•]. As noted above, there are no currently approved circulatory support devices that are able to adequately respond to the patient's metabolic demands.

Carmat (Carmat SA, Velizy Villacoublay, France)

The Carmat TAH is a novel, pulsatile device that consists of two chambers in which a bovine pericardium membrane separates a blood compartment from a hydraulic fluid compartment. Electrohydraulic pressurization of the membranes ejects blood through unidirectional bioprosthetic valves. This device is unique in that the blood contacting surfaces are biological, so these patients may not require anticoagulation [39]. In addition, preclinical bovine implantations with the Carmat device demonstrated the absence of significant blood trauma with a normal profile of von Willebrand factor and normal levels of clotting factors [40]. Four patients have been implanted with the device, and clinical investigation is ongoing [41]. Of note, the use of membranes may limit the long-term durability of this pump.

Fig. 2 BiVACOR TAH

Reinhart (Aachen, Germany)

The Reinhart TAH is another pulsatile device consisting of two pump chambers and a linear direct drive in between them. Flexible membranes separate the blood from the drive unit, which are moved to expel blood by two pusher plates. Interestingly, this device has been designed to act as a destination therapy device. Animal studies have shown that this device generated a cardiac output of 5 L/min and replaced the native heart function for up to 2 days [42].

RealHeart (Scandinavian Real Heart AB, Vasteras, Sweden)

Lastly, the RealHeart is pulsatile TAH designed to mimic native heart function. It consists of four chambers, two atria and two ventricles that are separated by valves. The device consists of two independently operated left and right pumps that create synchronous pulsatile outflow and continuous passive inflow. This TAH is also undergoing animal studies [43].

Use in Pediatric Population

The use of the TAH in the pediatric population is becoming increasingly relevant given the prevalence of complex congenital heart disease and the ongoing Syncardia 50 cc clinical trial. The use of ventricular assist devices in patients with complex congenital heart disease is limited due to physiologic and anatomic constraints. The TAH, on the other hand, can accommodate the anatomic and physiologic variation in some of these patients. There are handful of publications on the success of the TAH in bridging pediatric patients to transplantation [32, 44, 45]. In 2017, Morales et al. published the worldwide experience with the TAH in the pediatric population [46•]. From 2005 to 2015, 43 patients under the age of 21 (range 9 to 21 years) received a TAH for a variety of reasons. Ultimately, 58% of these patients were successfully bridged to transplantation.

Conclusion

As the burden of advanced heart failure continues to increase, the demand for mechanical circulatory support devices will continue to grow. LVADs are by far the most common devices implanted. However, with patients with or at risk for RV

failure, biventricular support is needed. Additionally, LVADs are not without complication, as RV failure, blood trauma, and progressive AI increase morbidity and mortality after implantation. In this patient population, and others, the TAH has been shown to be an important and effective option in patients awaiting transplantation, and possibly a better option in patients at high risk for post-LVAD RV failure and/or AI. Although there is currently one TAH on the market, there are many other next-generation devices being developed. These devices offer many advantages including physiologic response to increased metabolic demands, lower shear stress, improved durability, and elimination of complications related to retention of the native heart. With the increasing recognition of the advantages of total cardiac replacement and expansion to use as destination therapy, we may see an increase in the placements of total artificial hearts particularly if next-generation devices live up to their promise.

Compliance with Ethical Standards

Conflict of Interest Nathaniel Melton, Behzad Soleimani, Robert Dowling declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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