Heart failure remains the final common pathway of all forms of heart disease. Currently, more than 20 million patients suffer with heart failure in the US and Europe combined. Over the past two decades, advances in medical therapeutics have made inroads in reducing mortality associated with early- and mid-stage heart failure. Unfortunately, once patients progress to advanced heart failure, i.e., American Heart Association (AHA) stage D, New York Heart Association (NYHA) class IV, they face progressive and near-certain mortality. It is estimated that nearly 100,000 patients have advanced heart failure in the US. For these patients a ‘pump’ is needed to counteract circulatory failure, either in the form of a human heart transplant or a mechanical prosthetic device.

The SynCardia Temporary Total Artificial Heart (TAH) is the only TAH, despite 40 years of research and development by many groups, that has successfully passed the hurdles of rigorous clinical trials, US Food and Drug Administration (FDA) pre-market regulatory approval (PMA), and Centers for Medicare and Medicaid Services (CMS) reimbursement total artificial heart system available in the world today. The TAH is a complete, robust, pulsatile, biventricular replacement system indicated for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible biventricular failure. The TAH offers several advantages relative to present continuous flow left ventricular assist devices (LVADs), including higher ‘quality’ flow rates, reduced afterload and preload sensitivity, reduced thrombosis and stroke rates, and freedom from device-induced bleeding. More than 900 TAHs have been implanted to date, with a bridge-to-transplant success rate >79%. The availability of the new portable Freedom® driver has significantly enhanced patient mobility and made home discharge of patients possible. With home discharge, significant experience with long-term support on the TAH is now beginning to be accumulated. Technological advances continue to be imparted to the TAH system including portable driver enhancements, remote monitoring, and next-generation TAH designs.

**Advantages of the Total Artificial Heart Relative to Ventricular Assist Devices**

In the rapidly advancing field of mechanical circulatory support (MCS) it is becoming clear that there is need for a spectrum of devices able to address the varying degrees of cardiac dysfunction that are encountered in advanced heart failure. To date, a wide range of devices has been developed with varying pump capabilities, ranging from partial support, to ventricular assist, to full replacement. The SynCardia TAH is the only effective device in use in the world today that is capable of providing full cardiac replacement. If we examine MCS devices from the perspectives of intrinsic design, laboratory testing, and clinical trials, specific device features emerge that are distinctive and beneficial. From this perspective, the TAH has several unique features that are advantageous relative to VADs. The SynCardia TAH is a bi-ventricular pneumatic pulsatile pump consisting of three components: prosthetic ventricles (two), drivelines, and an external pneumatic driver (see Figure 1). Details of the TAH have been extensively described.

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Figure 1: Syncardia Total Artificial Heart

enhancements have been made to the SynCardia TAH system including advances in driver technology; TAH fabrication—with the development of TAH2; and remote monitoring of the TAH Freedom® 2 driver for patients discharged from the hospital to home. Further details of these advances will be described below. The TAH system was formerly known as the CardioWest™ and was officially renamed the SynCardia temporary TAH in 2010. This TAH received the CE Mark in Europe in 2003, FDA approval for use in the US in October 2004, and CMS coverage in May 2008. It remains the only fully approved TAH system in use today.

Of all MCS systems that exist, only the SynCardia TAH allows rapid and full hemodynamic restoration for the moribund patient. If it becomes clear for a given patient that heart recovery is not achievable, with transplantation or long-term device therapy the only possibility for salvage, then the SynCardia TAH will enhance organ perfusion and reduce backward failure to a degree superior to that of a left ventricular assist device (LVAD) or bi-ventricular assist device (BiVAD). Of all MCS systems available today, only the SynCardia TAH affords effective flows of >9.5L/min through both ventricles. The TAH can achieve such high flow rates with ‘quality of flow,’ with comparatively limited hemolysis and coagulation activation relative to modern rotary VAD systems that exist today.9 The TAH as a bi-ventricular replacement system provides full restoration of both the left and right heart function. What has emerged from clinical studies of modern rotary LVADs is that recovery and return of function occurs, however, sometimes with compromise. The compromise frequently is the unmasking of smoldering or evident right heart failure. If right heart function is not augmented with an additional VAD, to aid and support the right ventricle (RV), the patient may get by, but with a significant reduction in functional capacity and quality of life. Furthermore, if the patient converts to being supported by a dual-system BiVAD, they face a significant reduction in bridge-to-transplantation rate, with increased morbidity and mortality. The SynCardia TAH is a pulsatile system, in contrast with present VADs, which, for the most part are non-pulsatile, rotary devices. While the pros and cons of pulsatility for MCS device design have been debated for years, as pulsatility mimics the native heart, it offers both practical as well as theoretical advantages. On the practical side, the pulsatile SynCardia TAH is not as pressure- and volume-sensitive as rotary VADs. In clinical situations of hypertension and increased afterload, rotary VADs may have reduced flow and systemic perfusion, encountering difficulty overcoming forward impedance. Conversely, with hypovolemia and reduced volume status, rotary VADs may have a significant reduction in output. In contrast, the TAH, by virtue of its pulsatile nature, has adequate ejection force transfer and impact to overcome afterload, with its blood chamber reservoir allowing adequate fluid accumulation per beat, thereby having less volume sensitivity than a continuous flow blood pump.

On the theoretical side, pulsatility confers several advantages related to blood flow. Pulsatile blood flow has a reduced propensity for the development of turbulence.7 Further, pulsatility will delay the transition to turbulence if it occurs. Finally, pulsatility will allow re-laminarization of flow if turbulence occurs.8 Collectively, these features translate into less platelet activation and reduced risk for thrombosis. Pulsatile systems have also been shown to be associated with reduced inflammation, enhanced endothelial function, and, in the long run, maintenance of arterial integrity to a degree superior to non-pulsatile systems.9,10 The TAH as a pulsatile device is afforded many of these benefits.

A new limitation of modern rotary, non-pulsatile LVADs that has emerged is the occurrence of post-implant bleeding and hemorrhagic stroke. Several recent studies have demonstrated that these bleeding-associated events are related to the development of an acquired von Willebrand syndrome (AVWS) phenotype.12 The high shear encountered with the HeartMate II VAD has been shown to lead to denaturation of circulating large molecular weight von Willebrand multimers, reducing the ability of initial platelet monolayer formation associated with normal hemostasis. AVWS is not seen with the TAH as it generates pulsatile flow, coupled with flow through large orifices, which is largely free of protein denaturation effect.13

The development of progressive insufficiency of the aortic valve following rotary VAD implantation has also recently been observed.14 This has been attributed to progressive atrophy and biochemical alteration of the valve cellular and molecular composition as a result of loss of valve excursion and coaptation associated with left ventricular (LV) ejection. The consequence of this is flow regurgitation and loss of net forward output, with accompanying reloading of the compromised ventricle. This progressive decline in MCS function cannot occur with native heart removal and use of the TAH.

A major risk associated with VAD use is the possibility of embolization of occult thrombi present within the ventricle, present either at the time of implantation or subsequently post-implantation. Clinical experience has demonstrated that intra-ventricular thrombi are often not detectable, or under-detected, via conventional imaging modalities such as echo. Often, thrombi may be detected only with direct LV visual inspection at the time of VAD implantation. Even with this there is a heightened risk of not seeing or detecting thrombi which, with VAD implantation, may be readily mobilized and embolized. In contrast, if significant matted, friable thrombi are observed, with ventricular excision and TAH implantation the thromboembolic risk from LV thrombi is eliminated. The TAH has been observed to have a reduced thrombosis rate compared with many forms of MCS. In the pivotal clinical TAH trial, the observed stroke rate was 5%.1 In contrast, the stroke rate associated with VADs has ranged...
from 11 to 59%. This reduced thrombosis and embolization rate is largely due to intrinsic TAH design features, which include the large cavity volume of the TAH blood chamber, the significant degree of cavity washing associated with high flows, reduced flow turbulence, large cross-sectional area inflow and outflow valves, and the limited exposure of blood to foreign biomaterials by virtue of short prosthetic conduit path lengths.

The TAH has been demonstrated to completely obviate limitations that occur with LVAD use for certain clinical scenarios. For example, in a failing patient with a prosthetic aortic valve, LVAD use has been associated with increased thromboembolic risk. In this situation with unloading of the LV and non-ejection through the aortic valve, the prosthetic valve acts as a generator and nidus for thrombosis. Similarly, in the case of persistent arrhythmias, e.g. V Tach storm, net VAD pump function may be compromised. If a communicating defect, such as ventricular septal defect, is present, VAD function is also compromised. For these and other specific scenarios the TAH provides clear support advantage. Several clinical studies have further outlined situations in which the TAH offers clear advantage in terms of support and outcomes. These will be discussed below in the section covering device selection criteria.

**Summary of SynCardia Total Artificial Heart Clinical Experience**

The bulk of the world’s TAH experience has occurred with TAH devices built on the technology platform common to the present SynCardia TAH. The largest single-center experiences to date have been described in Arizona and Paris. From 1993 to 2002, 62 patients (51 men and 11 women) with irreversible bi-ventricular failure underwent implantation with the TAH in Arizona. Mean LV ejection fraction (LVEF) and central venous pressure (CVP) pre-implant were 20±8% and 20±7mmHg, respectively. The mean time on TAH support was 92±11 days (range 1–413 days). Seventy-seven percent of patients survived to transplantation with the TAH. Sixty-eight percent of the total group survived to discharge post-transplantation. Twenty-three percent of patients died during device support. Multi-organ failure caused 67% of these deaths. Adverse events included bleeding (20%), device malfunction (5%), fit complications (3%), mediastinal infections (5%), visceral embolus (1.6%), and stroke (1.6%). The linearized stroke rate was 0.068 events per patient-year.

A similar experience was reported by the group from Paris. To date, this group at Hospital La Pitié-Salpêtrière has the largest experience with the TAH. Between 1986 and 2001, 127 patients (108 males, mean age 38±13) underwent bridge to transplantation with the TAH. Mean arterial blood pressure and CVP pre-implant were 70±8mmHg and 27±8mmHg respectively. The duration of support increased progressively in the French experience, averaging two months after 1997, with a range of five to 271 days. One patient in their early experience was maintained on the TAH for 602 days, due to pre-implantation pre-formed anti-human leukocyte antigen (HLA) antibodies. Overall, 64% of patients survived to transplantation with the TAH. Twenty-three percent of patients died during device support; Multi-organ failure caused 67% of these deaths. The clinical thromboembolic event rate they observed was low, with no incidence of cerebrovascular accident (CVA) and only two transient ischemic attacks (TIAs). In all, they reported on a total experience of 3,606 implant-days, with only one instance of mechanical dysfunction.

The most robust experience published to date with the SynCardia TAH is the multicenter PMA trial experience. In this trial the hypothesis tested was that use of the TAH in patients with irreversible bi-ventricular failure would save lives, allowing for effective subsequent transplantation. Inclusion criteria for the study were: patients eligible for transplant, NYHA congestive heart failure (CHF) class IV, body surface area (BSA) range 1.7–2.5m², severe hemodynamic insufficiency. From 1993 to 2002 the TAH was implanted in 95 patients (81 protocol, 15 out-of protocol) with irreversible bi-ventricular failure, in imminent danger of death. Major efficacy end-points included rates of survival to transplantation, overall survival, survival after transplantation and ‘treatment success,' defined as: alive, NYHA class I or II, not on dialysis or a ventilator and ambulating. A control cohort of patients matched with those in the protocol group, without receiving a TAH, was used for contextual comparison.

In this study overall survival to transplantation was achieved in 79% of patients receiving the TAH versus 46% of the controls (p<0.001). Treatment success was achieved in 69% of the implant patients versus
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Figure 3: Registry Data Demonstrating the Percentage of Patients Stabilized on the Total Artificial Heart Being Successfully Bridged to Transplantation by Six Months

A

Implant dates: June 23, 2006–March 31, 2009
SyncCardia temporary Total Artificial Heart: n=50

Proportion of patients

Months after device implant

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

9% Alive with device in place
22% Dead
69% Transplanted

B

Implant dates: June 23, 2006–March 31, 2009
BIVAD: n=186

Proportion of patients

Months after device implant

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

11% Explanted (recovery)
23% Alive with device in place
31% Dead
35% Transplanted

BIVAD = bi-ventricular assist device.

37% of controls (p=0.002). The mean time from entry into the study to transplantation or death was 79.1 days for the implant group versus 8.5 days among the controls (p<0.001) (see Figure 2A). The overall survival rate at one year was 70% (95% confidence interval: 63–77%) in the group receiving an implant as per protocol compared with 31% in the control group (p<0.001) (see Figure 2B). Survival at one and five years after heart transplantation was 86 and 64%, respectively, compared with 69 and 34%, respectively, in the controls. These data compare favorably with the reported overall United Network for Organ Sharing (UNOS) survival data of 84.7% and 69.8% at one and five years, respectively.20

In the multicenter trial, significant improvement in secondary end-points was noted as well for the TAH group. Patients’ hemodynamic status immediately improved following placement of the TAH, with increased systemic pressure, reduced central venous pressure and increased organ perfusion pressure observed. Cardiac Index (CI) rose from a baseline pre-implant of 1.9l/min/m² to 3.2l/min/m². Renal and hepatic function and the levels of blood urea nitrogen (BUN), creatinine, bilirubin and transaminases returned to normal within three weeks of implantation. Electrolyte levels, white blood cell count and platelet count also normalized by three to four weeks post TAH implantation. Quality of life also improved for the TAH group. One week post-implant, 75% of these patients were out of bed. More than 60% of patients were able to walk more than 100ft at two weeks following implantation.

Seventeen of the 81 patients (21%) in the treatment group died before transplantation compared with 19 of the 35 control patients (54%). Causes of death in the treatment group were: multi-organ failure (seven patients), procedural or technical complications (four patients), bleeding (two patients), sepsis (two patients), congestive heart failure (one patient) and pulmonary edema (one patient). Causes of death in the control group prior to transplantation were: cardiac arrest (seven patients), heart failure (seven patients), multi-organ failure (three patients), acute rejection (one patient), and pulmonary edema (one patient).

Detailed recording of numerous potential adverse events was undertaken in this trial. The major adverse events reported, in addition to death, were bleeding, infection, neurologic dysfunction and device malfunction. In the implant group there were 102 bleeding events, 55 of which occurred after implantation, requiring ‘take back’ to the operating room for control. All but one of these procedures occurred within the first 21 days of implantation. Only two patients in this series died from bleeding. There were 125 infections recorded in the trial during use of the TAH, 50 being respiratory, 28 genitourinary (GU), 17 involving the driveline, 12 gastrointestinal (GI), seven blood-borne, six involving indwelling catheters and five mediastinal infections. In 68 of the 81 protocol patients (84%) these infections did not delay transplantation or contribute to death. All driveline infections were superficial, with none ascending to the mediastinum. Twenty-six neurologic events were noted in the protocol group, including stroke (11 events in 10 patients), transient ischemic attacks (four events), anoxic encephalopathy (five events), seizure (four events) and syncope (one event). Of the strokes observed, six of the 11 completely resolved without detectable residua after 48 hours, four had mild residua, with one having persistent hemiplegia. The linearized rate of stroke was 0.05 events per month. To date, this remains one of the lowest rates reported for any MCS device. One serious device malfunction was observed in the entire experimental cohort—that of a perforation of the pumping membrane. This occurred on day 124 post-implant, resulting in a patient death. No other serious device malfunctions have occurred during more than 12,000 patient-days of use of the TAH.

The TAH has found progressively increasing adoption and use both in the US and in Europe. Currently, the TAH is in use in over 40 medical centers worldwide. To date, more than 900 implants have been performed with the TAH. In several new US centers, not part of the original PMA trial cohort, significant adoption has occurred, with the TAH becoming a pivotal member of their MCS armamentarium for the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Level I and II heart failure patients. An example of this may be seen in the experience at Virginia Commonwealth University Medical Center (VCU). VCU initiated their TAH program in 2006 and to date have implanted 48 TAHs, with a >95% bridge-to-transplant rate. This center is
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cited as it is evidence that for a vital medical center interested in attaining the best patient outcomes, use of the TAH will achieve this goal.

In recent years, MCS device implantation and outcomes have been tracked by the INTERMACS. In the most recent published INTERMACS report, 76 TAHs have been tracked since March 2006. In a report issued in late 2009, registry data demonstrated that 69% of patients stabilized on the TAH had been successfully bridged to transplantation by six months, in contrast to only 35% of BiVADs and 25% of VADs (see Figure 3). These data demonstrate the efficacy of the TAH in recovering patients and successfully bridging them to transplantation. These results also highlight the efficiency in patient care achievable with the TAH, with TAH patients often advancing on the heart waiting list. These results are even more impressive when one considers that the TAH cohort was sicker than the BiVAD/VAD group, with 92% of the TAH cohort being INTERMACS level I and II, in contrast to 73% for the BiVAD and VAD group.

**Indication for Total Artificial Heart Use and Selection**

The present FDA indication for use of the TAH is as an in-hospital bridge to transplantation for patients who are transplant eligible with irreversible bi-ventricular failure in imminent risk of death. With the advent of the Freedom portable driver, allowing enhanced mobility and discharge home from the hospital, a goal is to broaden this indication. Currently on-going is the Freedom driver trial, recently approved for enrollment by the FDA (details below), which will afford extension of this indication in the US to allow home discharge.

Outside the US, the TAH is used for identical indications, as above, though with use outside of the hospital as well. Beginning in 2003, initial discharge home of bi-ventricular failure patients, stable on the TAH as bridge-to-transplant, was begun in Germany and subsequently in France. This was achieved through the development of a CE approved mobile 25lb driver system for the TAH, to demonstrate that TAH patients could be successfully discharged from the hospital and resume living. Following initial limited use under study, clinical use has expanded, with patients routinely going home once stable in many institutions throughout Europe today. Discharge to home has further been eased with replacement of this initial mobile driver with a much lighter and truly portable driver in Europe—the Freedom portable driver.

With home discharge has come increasing experience with long-term support. In Europe, in particular, with often greater than one-year transplant waiting times, a functional ‘destination by default’ scenario has occurred. Patients supported by the TAH for upwards of three years have been reported. In selected cases already in Europe, the TAH system has been employed as the definitive, i.e. destination therapy, for specific patients. With continued evolution of the SynCardia TAH (detailed below), including advancement of the TAH2 fabricated from polymeric materials, with extended wear life, and with progressive driver miniaturization, long-term therapy as an indication for this system is on the horizon.

The TAH has also been used both in the US and abroad as an acute bailout device for patients with irreversible cardiogenic shock associated with acute myocardial infarction (AMI). Once stabilized with a rapid-deployment MCS bridge-to-recovery system, e.g. TandemHeart™, the pathology of these myopathies is associated with reduced ventricular function and both diastolic and systolic dysfunction. Thickened, stiff ventricles present a particularly problematic situation is particularly problematic. Thickened, stiff ventricles present a problem for LVAD inflow cannulae placement and seating. Furthermore, the pathology of these myopathies is associated with reduced ventricular filling. As such, VADs are of limited use as the problem is more one of diastolic dysfunction, with reduced filling of the ventricle, as opposed to dilated systolic dysfunction of the ventricles, better served by VADs.

**Table 1: Total Artificial Heart Indications and Uses**

| Transplant-eligible (US) | AHA class D, NYHA class IV, INTERMACS level I or II |
|-------------------------|---------------------------------------------------|
| Hemodynamic insufficiency refractory to medical therapy |
| Irreversible bi-ventricular failure |
| Not a Candidate for Left Ventricular Assist Device as Evidenced by: |
| Right ventricular failure |
| Left ventricular thrombus |
| Refractory arrhythmias |
| Prosthetic aortic valve |
| Ventricular septal defect |
| Stone heart |
| End-stage infiltrative/restrictive cardiomyopathy |
| Transplant rejection/failure |
| Ventricular assist device failure |
| Un-resuscitatable cardiac arrest |
| Failure to wean from cardiopulmonary bypass with bi-ventricular injury |
| Surgical issues with massive myocardial infarction |
| Refractory cardiogenic shock |
| Poor outcome predictors: severe renal and hepatic dysfunction, ventilator |

AHA = American Heart Association; INTERMAS = Interagency Registry for Mechanically Assisted Circulatory Support; NYHA = New York Heart Association.

The use of the TAH in restrictive and infiltrative cardiomyopathies has emerged as an especially valuable indication, as LVAD use in this situation is particularly problematic. Thickened, stiff ventricles present a problem for LVAD inflow cannulae placement and seating. Furthermore, the pathology of these myopathies is associated with reduced ventricular filling. As such, VADs are of limited use as the problem is more one of diastolic dysfunction, with reduced filling of the ventricle, as opposed to dilated systolic dysfunction of the ventricles, better served by VADs.

In selecting the appropriate MCS device for a given patient, many factors must be considered in the decision-making process. First and foremost in considering the TAH is the presence of irreversible bi-ventricular failure. Beyond this, the nature of the myocardial substrate in specific situations, as outlined above, such as extensive LV wall necrosis associated with massive MI, tissue friability, ventricular thrombus, and restrictive myopathies, is best served with the TAH. Second, the issue of flow demand should be considered. In work undertaken by our group at the University of Arizona, as well as others, what has emerged is an algorithm related to CI. It has become clear that in order to salvage a
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Table 2: Left Ventricular Assist Device Mortality Risk Factor Profile Versus Total Artificial Heart Cohort Baseline

| Factor                          | Odds Ratio | Death TAH Cohort |
|--------------------------------|------------|------------------|
| Urine output <30ml/hour        | 3.9        | 67%              |
| BUN >40                        |            |                  |
| Central venous pressure >16mmHg| 3.1        | 40%              |
| Mechanical vent                | 3.0        | 35%              |
| PT >16s                        | 2.4        | 50%              |
| Reoperation                    | 1.8        | 33%              |

BUN = blood urea nitrogen; PT = prothrombin time; TAH = total artificial heart. Source: Oz et al., Circulation, 1995; 27 Farrar, J Heart Lung Transplant, 1994.

failing patient one must increase the CI from levels of 2 or less to levels above 2.5, or closer to 3. As CI is cardiac output divided by BSA, and as, unfortunately, individuals in today’s society are becoming larger with obesity, what is often needed is a device capable of flows in excess of 6l/min, i.e. closer to 8–9l/min. This is particularly important in the immediate post-implant period. This degree of flow can only be achieved, for the larger patient, with the TAH. Third, one must consider the ability of the device to fit in the thoracic cavity. For the TAH, a general guideline of BSA ≥1.7m² or an anteroposterior (AP) distance of ≥10cm from the anterior border of the vertebral body to the inner table of the sternum at T10 by computed tomography (CT) scan has been used, though experience exists with BSA down to 1.5m². In the near future, with the release of the TAH2, the heart will be available in two sizes: a 50cc heart in addition to the present 70cc version. This smaller TAH will extend the therapeutic window of TAH support to smaller adults and children, i.e. to individuals down to a body surface area of 1.2m².

Other factors to consider in choosing the TAH include the presence or possibility of right heart failure. This point is raised as a separate issue from clear initial bi-ventricular failure, as often RV failure emerges with time once on an LVAD. Having to then re-operate on the patient to place a right ventricular assisted device (RVAD) is associated with significant morbidity and mortality and overall reduced levels of bridge to transplantation and survival. Several clinical studies have identified variables recognized to be poor outcome predictors associated with LVAD use. Factors identified include reduced renal and hepatic function, coagulopathy and the need for persistent mechanical ventilation (see Table 2). Interestingly, in the pivotal TAH clinical trial, the TAH cohort, which had a bridge-to-transplant rate of 79%, had the exact profile recognized to be associated with poor outcomes with LVADs. We subsequently examined 52 risk factors in our entire five-center pivotal trial population as to their potential for being predictive of poor outcomes with the TAH. Interestingly, no single risk factor emerged as being predictive of poor outcomes with the TAH. This contrasts clearly to the above experience with VADs.

Total Artificial Heart Technology Advances—Enhanced Mobility, Home Discharge, Remote Monitoring, and Next-generation Designs

While the original SynCardia circulatory support system (CSS) driver has been successful in demonstrating the efficacy and viability of the TAH as a clinically effective therapy, its bulk has been a significant limitation (see Figure 4A). As a first step towards TAH system improvement, a new hospital replacement driver system, functionally equivalent to the CSS console, that is much lighter with an enhanced user interface and greater mobility, was developed. This system is known as the Companion driver and is CE marked and in use in many medical centers in Europe and Australia (see Figure 4B). FDA approval for the Companion driver will be applied for as a PMA supplement in the first quarter of 2011.

Beyond this, it has always been the goal of TAH therapy to return the patient to a fully functional status, allowing self-mobility and affording them quality of life with limited restriction. To achieve this goal, newer, smaller, truly portable drivers were a necessity. Hints of the possibility of this approach were seen several years ago with the development and deployment of the proof-of-concept 25lb mobile driver in Europe. However, a true dedicated driver, specifically designed for the SynCardia TAH, was needed. This driver now exists as the Freedom portable driver.

The Freedom driver is a wearable, electromechanical unit that is intended to provide pneumatic power for the implanted TAH, for use both in hospital and upon discharge home for clinically stable patients (see Figure 4C). The driver is a small unit approximately the size of a lunch box, weighing 13.5lb with two on-board, lithium ion rechargeable batteries. The driver may be carried in a shoulder bag or worn in a backpack. The driver generates pressure pulses of air through a driveline, resulting in movement of the TAH diaphragms, similar to that achieved with the CSS driver. The Freedom driver may be powered by either the on-board batteries in the drive unit housing, or by adaptors connected to external AC or DC power sources (wall power, the extended-life Freedom Power Pack or a car charger). A liquid crystal display (LCD) driver provides the user with left fill volume, cardiac output and device (beat) rate. Device rate, measured as beats per minute, is the only driver setting that is adjustable by the clinician on the Freedom. The Freedom is designed to provide pneumatic support for clinically stable TAH patients through adjustment only of the device beat rate.

The Freedom driver is CE approved in Europe and is in clinical use in several countries. With initial use of this driver, patients have reported feeling well, being self-ambulatory, with a significant return to normal function while at home. Several patients have returned to partial work activities, resumed driving, and had a return of sexual activity. In the US the Freedom driver is being studied under an investigational device exemption (IDE), having received FDA approval to conduct this investigation recently. This clinical study is intended to confirm the design verification test results that demonstrate that the Freedom driver system is a suitable replacement for the CSS console for clinically stable patients. Further, this study is being conducted to determine whether patients can cope with the TAH and Freedom driver out of the hospital, as has long been the case in Europe.

Up to 60 clinically stable TAH patients will be enrolled in this study. Of those, 30 are expected to be discharged from the hospital on Freedom driver system support. Subjects will be enrolled at up to 30 investigational sites. Subjects will be followed in the study from the date of initiation of Freedom driver system support until transplant, 90 days of Freedom driver system support, or death, whichever occurs first. The criteria for study success, i.e., that the Freedom driver is a suitable replacement for the CSS console for clinically stable patients, are that: (i) 90% of the subjects maintain an average cardiac index >2.0l/min/m² throughout
the duration of Freedom driver system support; and (ii) the overall adverse event profile that occurs while in the hospital while on Freedom driver system support is comparable to the adverse event profile from the PMA study for patients who would have met the enrollment criteria for the Freedom driver study. Adverse events will be collected according to the INTERMACS scheme. Currently patients are actively being enrolled in this investigation in the US. With TAH patients increasingly shifting to being at home, either as a bridge to transplantation or, for some, as long-term therapy, the utility of remote/home monitoring has emerged as a valuable added feature for the TAH system. As such, SynCardia has developed a simple, robust, user-friendly remote monitoring system. This system will be a feature in a second-generation Freedom driver, the Freedom 2. The Freedom 2 driver is expected to have a service interval of up to two years. Remote monitoring will be used to diagnose the remaining service life of the Freedom 2 driver, with the driver interrogated by the remote system.

With the view towards eventual use of the TAH for long-term support, and potentially as an alternative to heart transplantation, advances have been made in heart manufacture and fabrication. The TAH2 has been developed and is fashioned from enhanced, hemocompatible polymeric materials. These materials will allow simplification of TAH manufacture. In addition, they confer advantage to the TAH in terms of enhanced membrane durability. With the present design, membranes have proven durable; however, with the view of potential implant use for three to five years or beyond this proactive enhancement has been adopted. The TAH2 is expected to provide a significantly extended multi-year service life. This new version of the SynCardia TAH will undergo animal trials in the first quarter of 2011 and is expected to be submitted for approval to the CE in the second quarter of 2011. FDA submission will follow in the third quarter of 2011.

Emerging Clinical Demand for the Total Artificial Heart

Despite the growing clinical use of rotary VAD technology a persistent and growing need for the TAH exists. While VADs provide support for the failing patient they do not prevent the progressive nature of ventricular decline. The TAH remains the only MCS device capable of providing rapid and full hemodynamic restoration for a moribund patient. If a patient is categorized as INTERMACS level I or II with bi-ventricular failure, VAD use will not provide the same level of support and the rapidity and robustness of recovery as the TAH. In a study comparing 10 years of BiVAD use at the University of Pennsylvania, versus 10 years of TAH use at the University of Arizona, a bridge-to-transplant rate of only 46% was achieved with BiVADs versus a 77% rate with the TAH.5 The TAH is the only bi-ventricular replacement system that exists, and is in use today, with superior clinical efficacy. The TAH also offers the most robust blood flow, both in terms of amount of flow and quality of flow, available for any MCS device. This flow feature alone is often the difference between life and death for a given patient. Beyond these points the growth in demand for the TAH may be viewed from the perspectives of (i) patient demographics; (ii) technology limitations; and
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(ii) evolutionary improvement of the TAH. From the patient perspective, the overall population with heart failure is continuing to increase worldwide. As mentioned at the outset of this review, epidemiologic studies have revealed the presence of five million patients with heart failure currently in the US and nearly fifteen million in Europe. It is projected that these numbers will double over the next 15 years. Within this large population of patients, advanced heart failure—AHA class D, NYHA class IV—exacts a heavy toll. It is estimated that nearly 100,000 patients suffer from this advanced and fatal form of heart failure. This number is particularly alarming when one considers that heart transplantation, the definitive therapy for these patients, is performed in only 2,000 patients on average in the US each year—that is one out of every 50. As such, more than 90,000 patients succumb to this fatal disease. Even if one discounts the number of patients due to comorbidities and advanced age, a significant number of patients exists. For these patients a bridging device, salvaging and allowing robust recovery is needed. Beyond this, for many of these patients an alternative to transplantation is needed. With the limited availability of donor hearts and the decline in transplantation observed in recent years, a viable transplant alternative is needed. For both of these roles the TAH stands unique.

From the technology limitation perspective the VAD is not a substitute for the TAH. There are limits to VADS as they exist today. Despite improvements in VAD durability and performance, VADS in general do not have the pump output capabilities to match the pulsatile TAH. While some experimental work exists in attempting to use two rotary VADS as a TAH substitute, this still has many limitations. Leaving residual dysfunctional, thrombogenic and inflammatory cardiac tissue behind may eventually compromise systemic function and pump function. Furthermore, if cardiac tissue is excised securing two VADS, relative to the ease of implantation of the TAH this is an issue. With dual VADS inter-ventricular flow control is also an issue. Finally, the demonstration of acquired von Willebrand syndrome, as discussed above, will particularly limit the ability of these VADS to optimally function, especially at high flow rates. From an evolutionary perspective significant advances are in play and on the horizon for the TAH. As mentioned above a second-generation TAH (TAH2) is being tested, based on the current Syncardia TAH architecture, which incorporates advanced polymeric materials. These new fabrication materials have prolonged wear life, persistent flexibility and excellent hemocompatibility. The TAH being designed in both the current 70cc size as well as in a new, smaller 50cc size. The smaller heart will address the issue of the unmet need of a TAH system for smaller adults, especially women, and adolescents. Beyond this, a more advanced prototype of this heart has also been developed that is completely implantable, evolving beyond a pneumatic drive system. All of these features and perspectives support that the TAH will continue to be a vital and increasingly significant device in the ‘toolbox’ of mechanical circulatory support.

The Syncardia TAH has emerged as a robust form of mechanical circulatory support that has been demonstrated to be unique and life-saving for the sickest of heart failure patients. The TAH has shown superior efficacy in the treatment of irreversible bi-ventricular failure, in comparison with LVADs or BiVADs. The superior bridge-to-transplantation rate relative to BiVAD and many VAD systems, freedom from right heart failure, reduced morbidity and greater overall functional capacity are distinct features associated with the TAH. The emergence of increasingly miniaturized driver systems will continue to enhance and extend the functionality and utility of the TAH. Continued driver miniaturization will allow patients to be at home with a return to most life activities, affording them quality of life. The added feature of remote monitoring will allow early recognition of altered patient status, deviation in device function or driver decline. In the future, with the fabrication of the TAH from increasingly long-lasting polymer systems the potential of long-term TAH therapy, as a possible alternative to heart transplantation, is clearly on the horizon.

References

1. Heart Disease and Stroke Statistics – 2010 Update, Circulation, 2010;121:e46–215.
2. Syncardia Temporary CardioWest Total Artificial Heart (TAH) – P000111, FDA Approval Order, issued October 15, 2004, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmv/pma.cfm?num=p000111 (accessed February 17, 2011).
3. Artificial Heart Clinical Study Approvals, www.cms.gov/MedicareApprovedFacilitie/06_artificialhearts.asp (accessed February 17, 2011).
4. Copeland XL, Arabia FA, Tou PH, et al., Total artificial hearts: bridge to transplantation, Cardiol Clin, 2003;21:101–13.
5. Copeland XL, Smith RD, Arabia FA, et al., CardioWest Total Artificial Heart Investigators, Cardiac replacement with a total artificial heart as a bridge to transplantation, J Thorac Cardiovasc Surg, 2004;128:859–67.
6. Miller LW, Paganis FD, Russell SD, et al., for the HeartMate II Clinical Investigators, Use of a continuous-flow device in patients awaiting heart transplantation, J Thorac Cardiovasc Surg, 2007;133:585–94.
7. Ku DN, Blood flow in arteries, Ann Rev Fluid Mech, 1997;29:399–434.
8. Yousra EA, Berger SA, A turbulence model for pulsatile arterial blood flows, J Biomech Eng, 2004;126:578–84.
9. Loeb M, Koster A, Sänger S, et al., Inflammatory response after implantation of a left ventricular assist device: comparison between the axial flow MicroMed DeBakey VAD and the pulsatile Novacor Device, ASAIO J, 2001;47:272–7.
10. John R, Panich S, Hribal J, et al., Activation of endothelial and coagulation systems in left ventricular assist device recipients, Ann Thorac Surg, 2009;88:1171–9.
11. Nakano T, Tsuchiya M, Morita S, et al., Impacts of pulsatile systemic circulation on endothelium-derived nitric oxide release in anesthetized dogs, Ann Thorac Surg, 2003;75:156–62.
12. Uretz N, Pak SW, Jorde UP, et al., Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation, J Am Coll Cardiol, 2010;56:1207–13.
13. Heilmann C, Giessen U, Beyendorf F, et al., Acquired von Willebrand syndrome in patients with ventricular assist device or total artificial heart, Thromb Res, 2010;130:196–7.
14. Cowger J, Paganis FD, HoJ AI, et al., The development of aortic insufficiency in left ventricular assist device-supported patients, Circ Heart Fail, 2010;3:368–74.
15. Di Bella I, Paganis F, Bartha C, et al., Results with the Novacor Assist System and evaluation of long-term assistance, Europ J Cardio Thorac Surg, 2000;18:112–6.
16. Fraser GI, Rose EA, Gris ME, et al., for the HeartMate LVAD Investigators, Multi-center clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation, J Thorac Cardiovasc Surg, 2001;122:1186–95.
17. Slaughter MS, Rogers SJ, Milano CA, et al., for the HeartMate II Investigators, Advanced heart failure treated with continuous-flow left ventricular assist device, J Thorac Cardiovasc Surg, 2009;138:2141–51.
18. Copeland XL, Smith RD, Arabia FA, et al., Total artificial heart bridge to transplantation: a 9-year experience with 62 patients, J Heart Lung Transplant, 2004;23:833–31.
19. Littrup P, Benoit N, Rama A, et al., Bridge to transplantation with the iVAD-F (CardioWest) total artificial heart: a single center 15-year experience, J Heart Lung Transplant, 2003;22:1296–305.
20. 2001 Annual report of the U.S. Organ Procurement and Transplantation Network and the scientific Registry of Transplantation Recipients, Vol. 1, Washington, DC: Department of Health and Human Services, 2001:429–83.
21. INTERMACS Quarterly Statistical Report, www.uab.edu/ctsresearch/intermacs/statisticalsummaries.htm (accessed January 17, 2011).
22. INTERMACS Selected PowerPoint Slides, issued 3/31/09, www.uab.edu/ctsresearch/intermacs/statisticalsummaries.htm (accessed February 17, 2011).
23. Syncardia Total Artificial Heart – Indications for use, www.fda.gov/ohrms/dockets/ac/04/briefing/042001b_final.pdf (accessed February 17, 2011).
24. Stepien MI, Copeland XT, The Total Artificial Heart in refractory cardiogenic shock: saving the patient versus saving the heart, 11th Int Pac Cardiovasc Med, 2008;5:45–5.
25. Leprince P, Benoit N, Vannous S, et al., Patients with a body surface area less than 1.7m² have a good outcome with the CardioWest Total Artificial Heart, Heart Lung Transplant, 2005;24:1501–6.
26. Dang NC, Topkara VK, Mercandó M, et al., Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure, J Heart Lung Transplant, 2006;25:1–6.
27. Co MC, Goldstein DJ, Pepino P, et al., Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices, Circulation, 1995;92:169–73.
28. Fette DJ, Preoperative predictors of survival in patients with Thoratec ventricular assist devices as a bridge to heart transplantation: Thoratec Ventricular Assist Device Principal Investigators, J Heart Lung Transplant, 1994;13:93–101.
29. Copeland XL, Smith RD, Rosse RW, et al., Risk factor analysis for failure to transplantation with the CardioWest total artificial heart, Ann Thorac Surg, 2008;85:1639–44.
30. Leinhoven BS, Smith RD, Ghani AA, et al., Is the Total Artificial Heart Superior to BiVAD Therapy as a Method of Bridging Patients to Heart Transplantation? 43rd Annual meeting of the Society of Thoracic Surgeons, San Diego, CA, January 2007.
31. Roger VL, The heart failure epidemic, in J Elinson Res Public health, 2010;1:1807–30.